USE OF BIS-PHOSPHINE PLATINUM-DICATIONS AS HIGHLY ELECTROPHILIC CATALYSTS FOR GENERATION OF INTERMEDIATE CARBOCATIONS IN CATALYSIS

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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

2007

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ABSTRACT

CHARLES A. MULLEN: Use of Bis-Phosphine Platinum-Dications as Highly Electrophilic Catalysts for Generation of Intermediate Carbocations in Catalysis
(Under the Direction of Michel R. Gagné)

Chiral Pt-dicationic catalysts capable of C-C bond formation with the intermediacy of carbocations were developed. Similar carbocations are key intermediates in the biosynthesis of terpenoid natural products, and are normally generated by protonation of an alkene or an epoxide under careful enzymatic guidance. Under non-enzymatic conditions such activations of alkenes are much more difficult to control. Synthetic Pt-dicationic complexes were developed for selective generation of these key intermediates in two specific types of processes. One, the asymmetric Prins cyclization reaction, and second an asymmetric oxidative cation-olefin cascade cyclization reaction that converts polyolefin substrates into complex polycyclic products, an analogy to steroid biosynthesis.

Highly electrophilic P_2Pt^{2+} catalysts proved to be uniquely able to catalyze a Prins cyclization reaction in the reaction of alkenyl phenols and glyoxylate esters. Other chiral Lewis acids provided the products of a concerted glyoxylate-ene reaction. The uniqueness of the reactivity to Pt-dicationic catalysts suggested that they were able to access trappable ionic intermediates. This reaction was made highly enantioselective by employing (*tol*-BINAP)Pt^{2+} catalysts and tBu glyoxylate with various phenol substrates.

The P_2Pt^{2+} catalysts also proved capable of mediating regio- and diastereoselective oxidative polycyclization reactions of dienol and trienol susbtrates. This biomimetic cyclization is initiated by Pt(II) activation of a less substituted alkene at the terminus of a polyene susbtrate and is terminated by β-hydride elimination. This transformation was rendered catalytic by employing trityl cation to abstract hydride from the putative cationic Pt-hydride to regenerate the Pt^{2+} catalyst. Good enantioselectivity could be achieved in this reaction by employing xylyl-PHANEHPOS as the bisphosphine ligand.

To Shawn

ACKNOWLEDGEMENT

First and foremost, I have to thank my Mike Gagné for being an outstanding and enthusiastic research advisor. He has a great ability to see the positive side of many seemingly negative results and that proved inspirational to me when things weren't going particularly well. I also have to thank my lab-mates for making the work day (and night) a pleasant (or at least interesting) place to be. I particularly have to thank Jeremy (Doosh) for going through all the battles of these 5 years with me. I was very fortunate to go through all this with him as a great friend and coworker; it surely made things easier. I also have to thank the other friends who work or have worked here with me including Will Kerber, Mike "Nailz" Doherty, and Mike Tarselli. I also have to thank the crew of current 5th year grad students who have been the life to the parties of my time in Chapel Hill.

I also have to thank my parents and family for their encouragement and support. But most of all I have to thank my soon to be wife, Shawn for her unconditional love and support. We've been "together" through all of this and I am anxious to loose the quotes. It has been tough on both of us at times spending so much time apart, but I know it will make the time ahead we have together that much better. I could not have done this without you.

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LIST OF ABBREVIATIONS

2D	two dimensional
3°	tertiary
Å	angstrom
AcOH	acetic acid
Ar	aryl
BINOL	1,1'-bi-2-naphthol
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Bu	butyl
BQ	benzoquinone
°C	degrees Celsius
cm	centimeters
COD	1,5-cyclooctadiene
Cp	cyclopentadienyl
d	doublet
dd	doublet of doublets
dppe	1,2-bis-(diphenylphosphino)ethane
dr	diastereomer ratio
DTBP	ditertbutyl pyridine
ee	enantiomeric excess
endo	endocyclic

eq	equation
equiv.	equivalent
Et	ethyl
EtOAc	ethylacetate
exo	exocyclic
g	gram
GC	gas chromatography
h	hour
HOTf	trifluoromethanesulfonic acid
HR	high resolution
Hz	hertz
(I)	monovalent
(II)	divalent
*i*Pr	isopropyl
J	three-bond H-H coupling constant
$J_{P\text{-}Pt}$	one-bond P-Pt coupling
K	Kelvin
kcal	kilocalorie
KIE	kinetic isotope effect
LA	Lewis acid
m	multiplet
m	meta
M	molarity
M^+	molecular ion
Me	methyl

mg	milligram
MHz	megahertz
M(I)	monovalent metal
M(II)	divalent metal
MeOH	methanol
min	minutes
mL	milliliter
mmol	millimole
mol	mole
mol%	molar percentage
MS	mass spectrometry
m/z	mass-to-charge ratio
N	normality
NEt_3	triethylamine
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
o	ortho
ORTEP	anisotropic displacement ellipsoid plot
p	para
P_2	bisphosphine
Ph	phenyl
Ph_2NMe	N,N-diphenylmethylamine
PNP	2,6-bis-(diphenylphosphino)methyl)pyridine
ppb	parts per billion

ppm	parts per million
PPP	bis-(2-diphenylphosphinoethyl) phenylphosphine
psi	pounds per square inch
PTFE	polytetrafluoroethylene
q	quartet
rac	racemic
RT	room temperature
s	singlet
SFC	super critical fluid chromatography
t	triplet
t_R	retention time
tBu	tertbutyl
td	triplet of doublets
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
μL	microliter

Chapter 1

Cation-Olefin Cyclizations: Inspiration from Nature

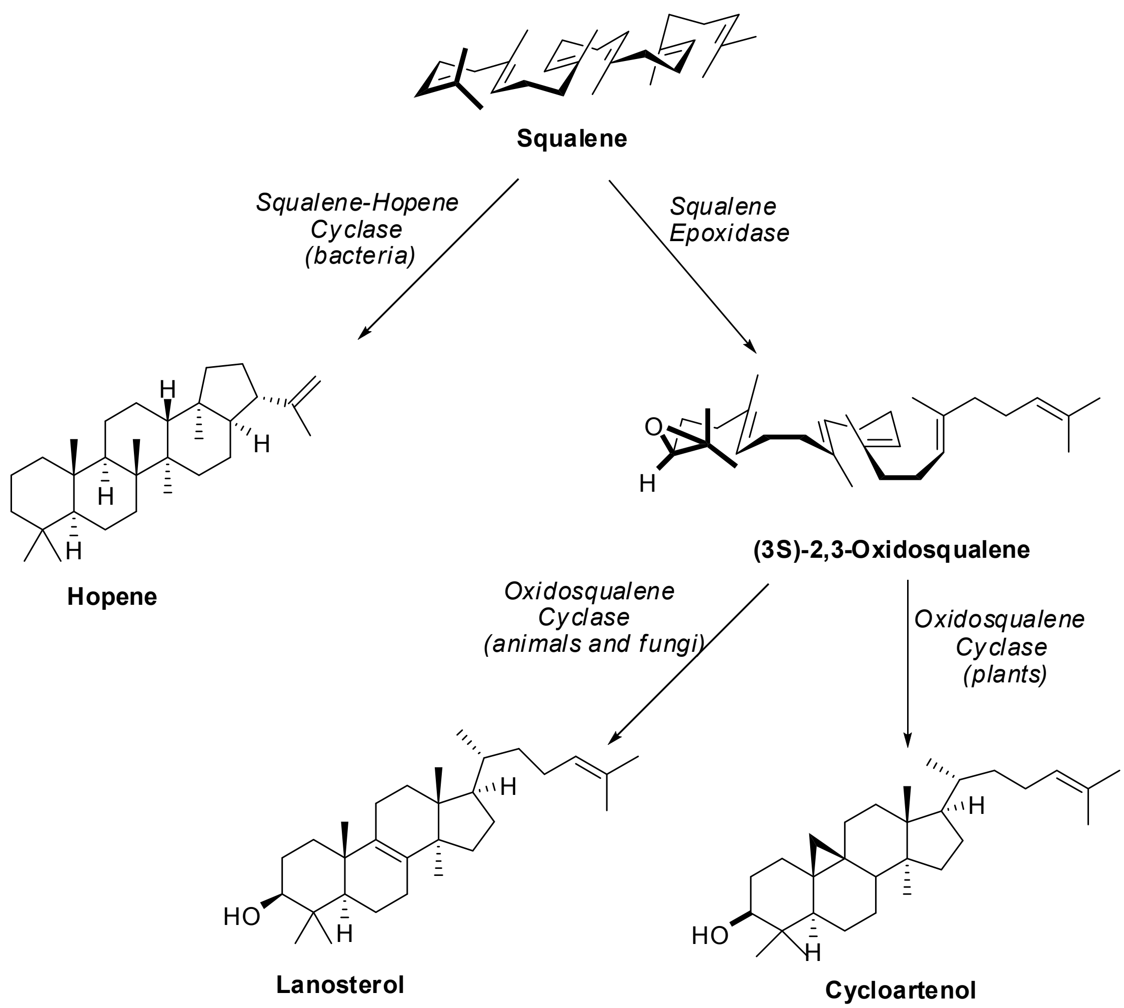
1.1 Enzymatic Cyclization of Squalene and Squalene Derivatives

For pure synthetic efficiency, one of the most impressive biochemical transformations known is the enzyme-catalyzed cyclization of triterpenes, a ubiquitous reaction found in nature in organisms ranging from simple microbes to plants and animals.[1] In these processes, carbon-carbon bond formation via cation-olefin reactions creates tetra- and penta-cyclic products from open chain polyolefin precursors. The power of these reactions is illustrated by the various architecturally different products that enzymes can make remarkably efficiently and selectively from the common precursor, squalene (Scheme 1.1). In plants, animals and fungi, squalene is enantioselectively epoxidized by squalene epoxidase to afford (3*S*)-2,3-oxidosqualene. There are numerous oxidosqualene cyclases and each is capable of generating unique natural products including lanosterol and cycloartenol. Bacteria do not epoxidize squalene prior to cation-olefin cyclization; rather squalene-hopene cyclase catalyzes an enantioselective, diastereoselective polycyclization initiated by proton transfer to the alkene at the terminus. It is believed

1. (a) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem. Int. Ed.* **2000**, *39*, 2812 – 2833. (b) Abe, I.; Rhomer, M.; Prestwhich, G. D. *Chem. Rev.* **1993**, *93*, 2189 – 2206. (c) Yoder, R. A.; Johnston, J. N; *Chem. Rev.* **4730**, *105*, 4730 – 4756.

that bacterial squalene-hopene cyclase is the common ancestor of which all the oxidosqualene cyclases have evolved.[1c]

Scheme 1.1



A large number of cyclic products are energetically competitive from a cationic reaction of a polyolefin such as squalene or oxidosqualene because formation of a 6-membered ring by intramolecular olefin addition to a carbocation is exothermic (ca. -20 kcal/mol) and has a low barrier to activation (ca. 1 kcal/mol).[2] Therefore, strict conformational control of the polyene substrate via substrate preorganization by the

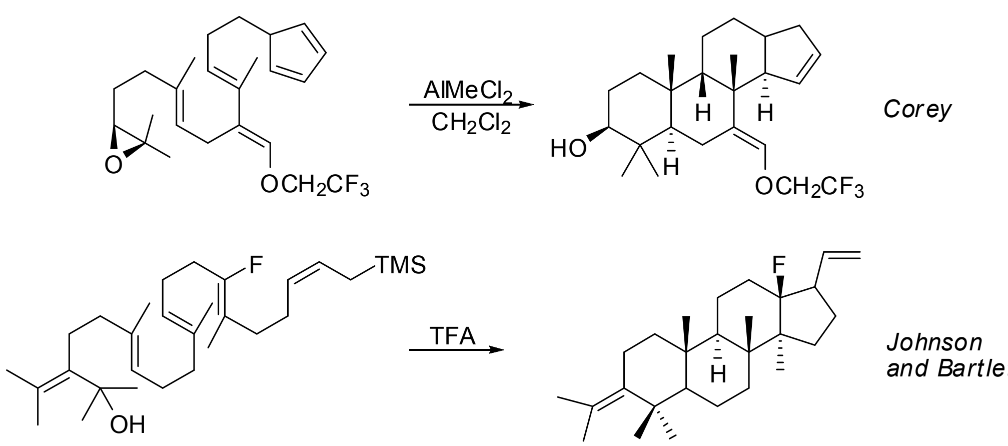
2. Jenson, C.; Jorgensen, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 10846 – 10854.

enzyme active site is required for high product selectivity. For example, when oxidosqualene is converted to lanosterol, oxidosqualene is preorganized into a chair-boat-chair conformation (as depicted in Scheme 1.1) prior to cyclization initiation via epoxide ring opening.

1.2 Biomimetic Cation-Olefin Reactions

Because of the high efficiency and selectivity afforded by enzymatic polyolefin cyclization, chemists have strived to develop synthetic processes that employ electrophilic reagents to activate polyolefins. Classic methods developed for this purpose include activation of epoxides or acetals and dehydration of tertiary alcohols.[3,4]

Scheme 1.2



3. (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1-8. (b) Johnson, W.S. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9-17. (c) Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587 - 9595. (d) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765 – 8766. (e) Corey, E. J.; Lee, J.; *J. Am. Chem. Soc.* **1993**, *115*, 8873 – 8874. (f) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290 - 11291. (g) Corey, E. J.; Wood Jr., H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982-11983.

4. For examples of enantioselective synthetic cation-olefin polycyclizations see Section 3.1.

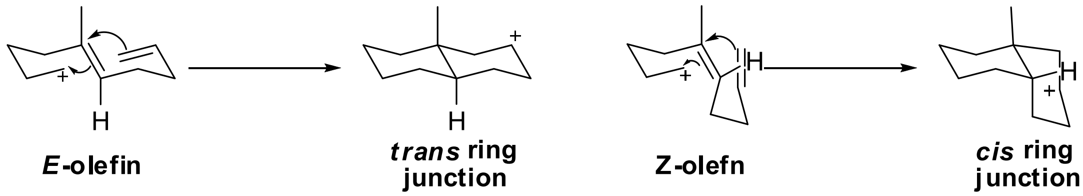


Figure 1.1. Stork-Eschenmoser postulate.

In the absence of an enzyme active site, the stero- and regiochemistry of cation-olefin reactions is necessarily dictated by the relative energetics of polyene conformers in solution. The basis for diastereoselectivity in cation-olefin reactions is the Stork-Eschenmoser postulate,[5] which states that the stereochemistry of a ring junction is determined by the geometry of the alkene from which it was formed (Figure 1.1). For terpene structures, this leads to *trans-anti-trans* relative stereochemistry as a series of 6-membered chair transition states to construct the polyene structure (Figure 1.2).

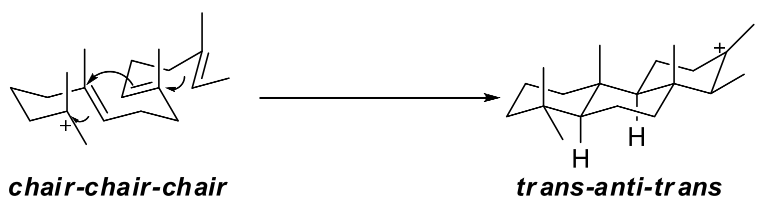


Figure 1.2. Cyclization of terpenes through chair transition states leading to *trans-anti-trans* ring junctions.

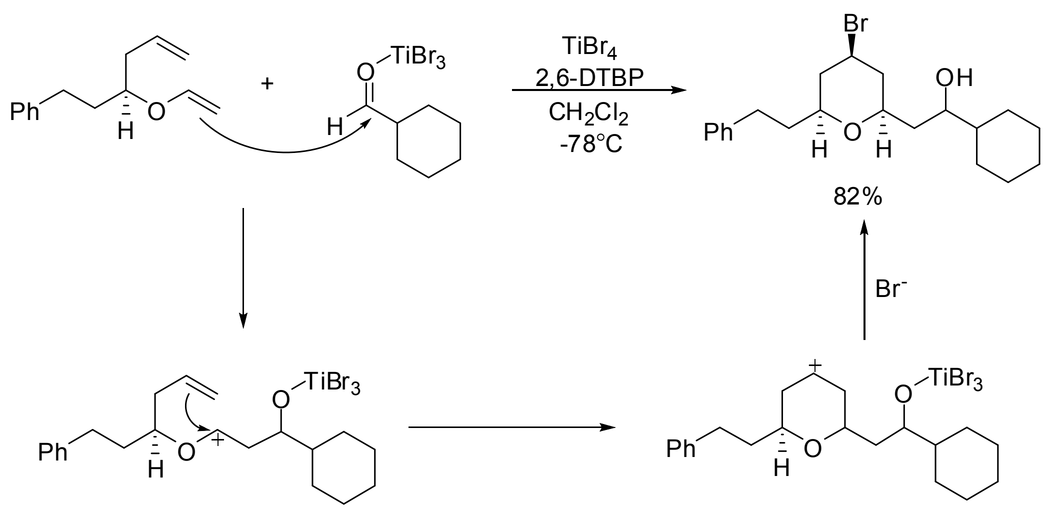
1.3 Cation Generation via Intermolecular Carbon-Carbon Bond Formation

A key step to biomimetic polycyclization is selective cation generation. The examples in Scheme 1.2 use the technique of placing functional groups in strategic positions on the molecule so that activation of those groups leads to cation formation at the desired location. Another means to generate a cation from an olefin is through an intermolecular carbon-carbon bond forming reaction with an electrophilic carbon source

5. (a) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068-5077. (b) Eschenmoser, A.; Ruzika, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta.* **1955**, *38*, 1890-1904.

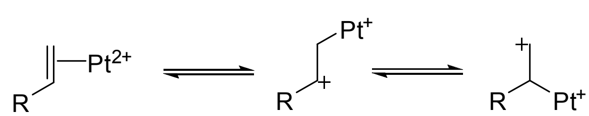
such as an activated carbonyl. Rychnovsky has reported a $TiBr_4$ mediated Prins reaction[6] where intermolecular attack of a vinyl ether on an activated aldehyde results in an oxocarbenium ion (Scheme 1.3). Intramolecular trapping of the oxocarbenium ion by another alkene generates a cyclic cation followed by subsequent trapping by Br^- to complete the reaction.

Scheme 1.3



1.4 Cation Generation via η^2-alkene Coordination to Pt^{2+}

Highly electrophilic Pt^{2+} complexes selectively coordinate to less substituted alkenes over more highly substituted alkenes. This η^2-alkene coordination to Pt^{2+} can be thought of as an equilibrium of an η^1 Pt-alkyl species with a β carbocation (eq. 1.1)

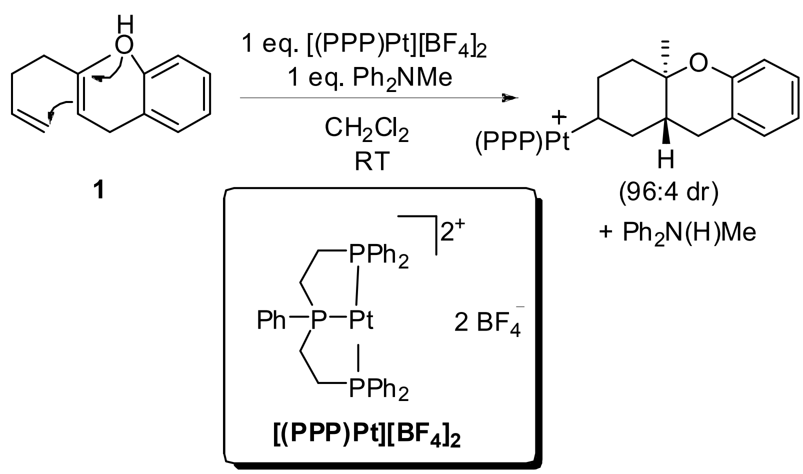


(1.1)

6. Patterson, B.; Marumoto, S.; Rychnovsky, S.D. *Org. Lett.* **2003**, *5,* 3163 – 3166.

Cyclogeneration of a subsequent carbocation has been proven possible when 1,6- and 1,7-diene substrates are activated in this fashion.[7] When β-hydride elimination inhibiting pincer ligated (PPP)Pt^{2+} is used to activate dienol substrate **1** a stable cationic polycyclic Pt-alkyl species is formed (Scheme 1.4).[6a] In this case, activation of the monosubstituted alkene led to carbocyclization to generate a tertiary carbocation that was trapped by the phenol.[8]

Scheme 1.4



1.5 Research Objectives

With selective carbocation generation key to initiation of biomimetic cation-olefin polycyclizations, we looked to generate carbocations by the methods described in Sections 1.4 and 1.5. We hypothesized that useful functionalized polycyclic products could be obtained through reaction of a polyenol with a Lewis-acid activated carbonyl (eq 1.2). Furthermore, since chiral Lewis acids are well known to achieve to high

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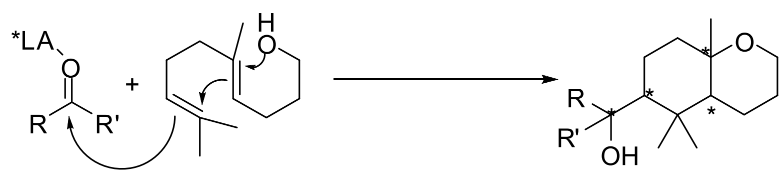
7. (a) Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3459 – 3641. (b) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013-3015. (c) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379 – 3381. (d) Feducia, J. A.; Campbell, A. N.; Doherty, M. Q.; Gagné, M. R. *J. Am. Chem. Soc.* **2006**, *40*, 13290 – 13297.

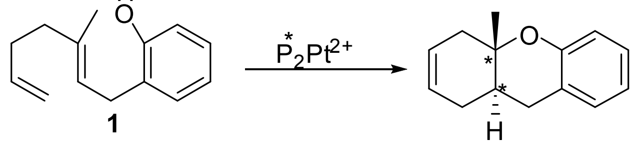
8. For a more in depth discussion of this reaction and its stereochemistry see Section 3.1

enantioselectivity when activating prochiral carbonyl species, this was a potential route to an asymmetric polycyclization. Key to generating cations via this method is to generate enough electophilicity through the Lewis acid/carbonyl combination to support carbocationic intermediates to overcome competitive concerted pericyclic reactions (i.e. the carbonyl-ene reaction). Work towards generation of such carbocationic intermediates is presented in Chapter 2.



(1.2)

Previous work had demonstrated proof of principle that phosphine ligated Pt-dications were capable of initiating cation-olefin cyclizations (Scheme 1.4). This represented a polycyclization potentially amenable to asymmetric catalysis via the use of chiral phosphine ligands; however, turnover to a viable catalytic cycle had not yet been achieved. We looked to a simpler catalyst system employing P_2Pt^{2+} catalysts. This makes employing a chiral ligand easy, with a large number of chiral bisphosphines readily available. Additionally, removing the pincer ligand allows β-hydride elimination to occur and for the polycyclic product to be liberated from the metal (eq. 1.3). Studies towards discovering a highly selective catalyst and generating efficient turnover are presented in Chapter 3.



(1.3)

Chapter 2

Asymmetric Prins Cyclizations

2.1 Introduction

The Prins reaction is the nucleophilic addition of an alkene to an aldehyde with the generation of a cation that subsequently rearranges or is trapped.[1] When used in an intramolecular mode, Prins cyclizations are capable of generating a wide variety of heterocycles, usually with net addition of an external nucleophile to the resulting carbocation.[2] Prins reactions can also be terminated by trapping though a pendant nucleophile[3] or through a pinacol rearrangement.[1c]

Mechanistically related to the Prins reaction is the carbonyl-ene reaction, wherein a proton from the nucleophilic alkene is transferred to the developing charge on the carbonyl oxygen, thus generating a homoallylic alcohol (Scheme 2.1). Several lines of evidence (both

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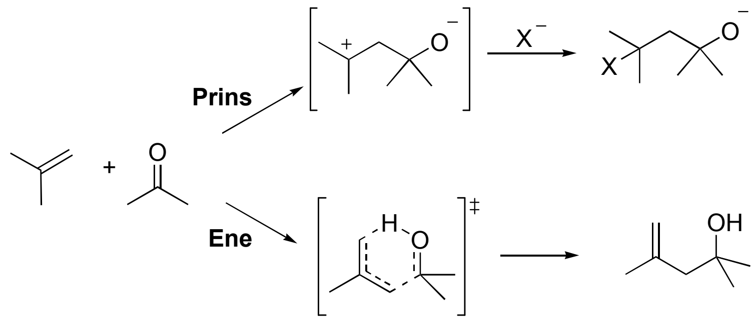
1. For Prins Reaction Reviews see: (a) Adams, D.R.; Bhatnagar, S.P. *Synthesis* **1977**, 661-672. (b) Sinder, B. In *Comprehensive Organic Chemistry*; Trost, B. M. Ed.; Pergamon Press: New York, 1991; Vol. 2, pp 527-561. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143-7157.

2. For some recent examples see: (a) Delgard, J.E.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 15662-15663. (b) Jasti, R.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2004**, *126*, 9904-9905. (c) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramíez, M. A.; Martín, V. S. *J. Org. Chem.* **2005**, *70*, 57-62. (d) Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Bermejo, J.; Martin, V. S. *Org. Lett.* **2003**, *5*, 1979-1982. (e) Yang, X.; Mague, J. T.; Li, C. *J. Org. Chem.* **2001**, *66*, 739-747. (f) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tet. Lett.* **2005**, *46*, 2133-2136. (g) Yu, C.; Yoon, S.; Hong, Y.; Kim, J. *Chem. Commun.* **2004**, 1840-1841. (h) Chan, K. P.; Loh, T. P. *Tet. Lett.* **2004**, *45*, 8387-8390. (i) Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499-1502.

3. Mikami , K.; Shimizu, M. *Tetrahedron* **1996**, *52*, 7287-7296.

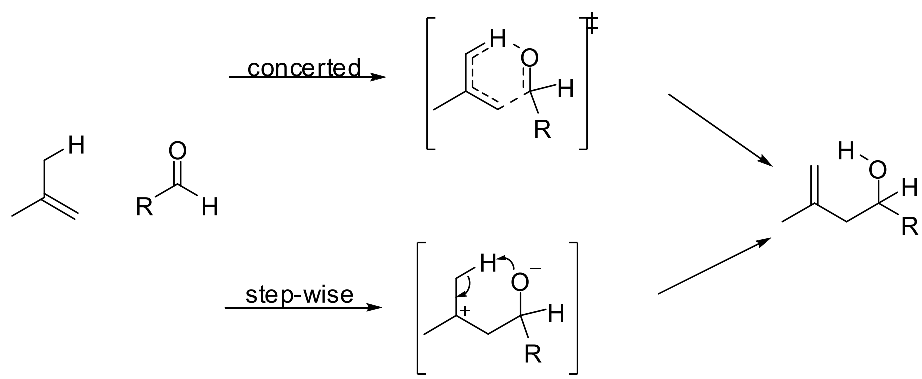
Scheme 2.4



experimental[4] and computational[5]) suggested that in contrast to thermal conditions, Lewis acid accelerated –ene reactions[6] could proceed via stepwise mechanisms, through a discrete cationic intermediate prior to proton transfer (Scheme 2.2).

One such study compared kinetic isotope effects of a thermally induced –ene reaction of 2-methallylbenzene and oxodiethyl malonate (Scheme 2.3).[4d] The observation of

Scheme 5.2



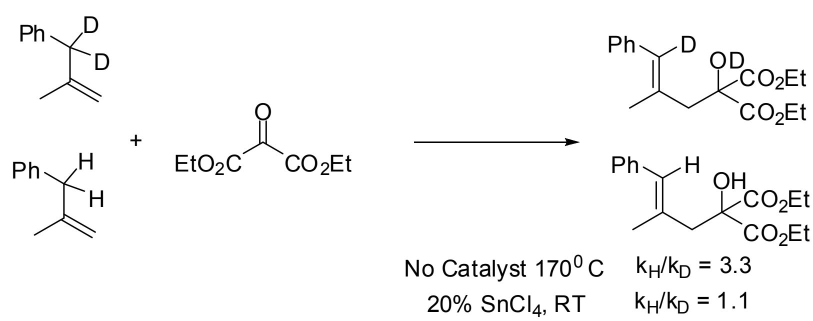
4. Mikami, K.; Wakabayashi, H; Nakai, T. *J. Org. Chem.* **1991**, *56*, 4337-4339. (b) Song, Z.; Beak, P. *J. Am. Chem. Soc.* **1990**, *112*, 8126-8134. (c) Snider, B. B.; Ron, E. *J. Am. Chem. Soc.* **1985***, 107*, 8160-8164. (d) Stephenson, L. M.; Orfanopoulos, M. *J. Org. Chem.* **1981**, *46*, 2200-2201.

5. Yamanaka, M.; Mikami, K. *Helv. Chim. Acta*. **2002**, *85*, 4262-4271. (b) Mikami, K.; Ohmura, H.; Yamanaka, M. *J. Org. Chem.* **2003**, *68*, 1081-1085. (c) Morao, I.; McNamara, J. P.; Hillier, I. H. *J. Am. Chem. Soc.* **2003**, *125*, 628-629.

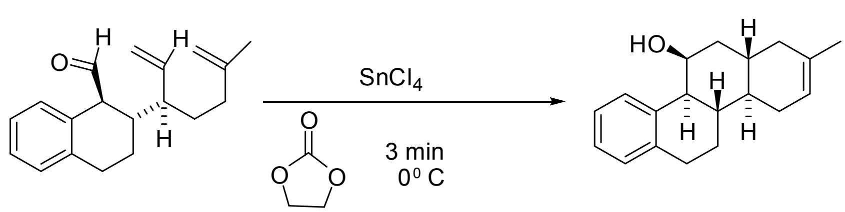
6. For reviews on the -ene reaction, see: (a) Mikami, K.; Nakai, T.; In *Catalytic Asymmetric Synthesis, Second Edition*; Ojima, I., Ed.; Wiley-VCH: New York, NY, **2000**; pp 543-568. (b) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305-342. (c) Santelli, M.; Pons, M. *Lewis Acids and Selectivity in Organic Synthesis;* CRC Press, Inc.: Boca Raton, FL, **1995**.

a kinetic isotope effect of 3.3 for the thermal reaction and virtually no isotope effect for the catalyzed reaction suggested that proton transfer to the carbonyl oxygen was involved in the rate determining step of the reaction in the thermal case and not involved in the catalytic case. This suggested that in the catalyzed reaction carbon-carbon bond formation is rate-determining and is followed by a rapid proton transfer; while in the thermal case a concerted pathway is followed.

Scheme 2.6



Conceptually related to this notion is the reaction shown below, which was simply termed a Lewis acid catalyzed –ene reaction, but given the possibility of step-wise reactivity, it could also result from interception of an intermediate cation (eq. 2.1).[7] Ethylene carbonate was found to be the optimal for good yields of product, providing circumstantial evidence for the involvement of cations.[8]



(2.1)

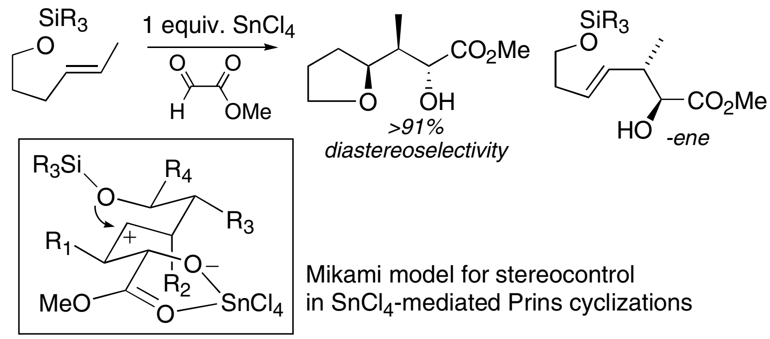
Another relevant example is the $SnCl_4$-mediated Prins cyclization of silyl protected pentenols (Scheme 2.4).[3] Mikami noted that Me_2iPrSi- protecting groups optimally provided

7. Zielgler, F. E.;Wang, T. F. *J. Am. Chem. Soc.* **1984**, *106*, 718-721.

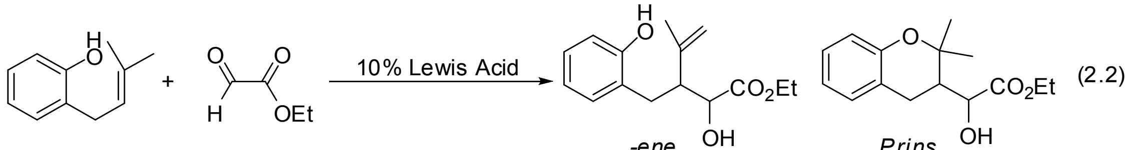
8. Ethylene carbonate is a key cosolvent in many of the cationic cyclizations developed by W. S. Johnson: McCarry, B. E.; Markezich, R.; Johnson, W. S. *J. Am. Chem. Soc.* **1973**, *95*, 4416-4417.

the Prins product with the –ene product being a minor byproduct (<30%). Other combinations of protecting groups, tether length, and Lewis acid either led to decomposition or –ene products. Based on the effect of substitutents on the cyclization diastereoselectivity, a model explaining each position's orientational preference was presented.

Scheme 2.7



While many excellent catalysts have been developed for enantioselective ene-reactions (and especially for glyoxylate-ene reactions[5,9]), an asymmetric variant of the Prins cyclization was unknown. We reasoned that a suitable catalyst could generate a trappable form of the step-wise –ene reaction intermediate cation, and therefore initiated a search for such a species. We began our investigation with the Lewis acid catalyzed reaction of 2-prenyl phenol (**1**) and the chelating aldehyde ethyl glyoxylate. While most of the Lewis acids provided predominantly the –ene product **2**, (bisphosphine)Pt^{2+} ligands provided chroman **3 (**eq 2.2). Refining the catalyst and reaction conditions led to a highly enantioselective variant.



1 **2** **3b** (2.2)

9. Examples with various catalysts: (a) Mikami, K.; Terada, M.; Nakai, R.; *J. Am. Chem. Soc.* **1990**, *112*, 3949-3954. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc.* **2000**, *122*, 7936-7943. (c) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059-4062. (d) Koh, J. H., Larsen, A. O.; Gagné, M.R. *Org. Lett.* **2001**, *3*, 1233-1236.

This chapter describes the development of catalyst and conditions for this reaction, scope, limitations and some mechanistic detail of this unique example of an enantioselective Prins reaction.

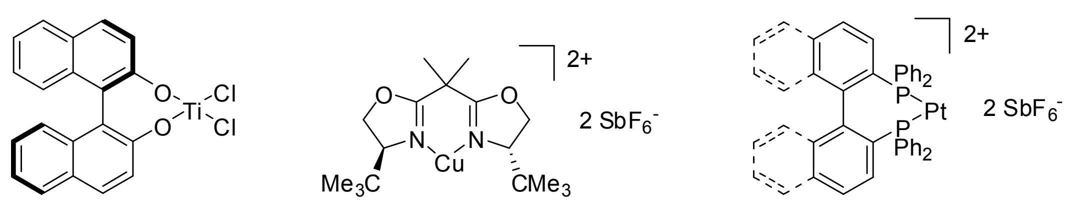
2.2 Results and Discussion

A. Catalyst Development. A variety of Lewis acids known to be excellent catalysts for the glyoxylate-ene reaction were screened (Table 2.1) for the reaction of 2-prenyl phenol (**1**) and ethyl glyoxylate. In most cases, the major compound was the glyoxylate-ene product **2**, indicating that with these catalysts, proton transfer is either too fast for efficient trapping by the phenol or that the overall process occurs without the intermediacy of a putative electrophilic alkenyl carbon. Interestingly, the Cu(II)^{t}BuBOX-catalyzed glyoxylate-ene reaction, which computationally proceeds via a cationic intermediate,[5c] provides the –ene product almost exclusively. The highly enantioselective (BINOL)TiX_2 catalysts were completely unreactive with these substrates. In contrast to each of these established catalysts, P_2Pt^{2+} catalysts were uniquely able to generate the chroman **3** as the sole product.

Table 2.1. Ratio of Prins:Ene Products as a Function of Catalyst[a]

Catalyst	3:2
(BINOL)$TiCl_2$	--
$Cu(OTf)_2$	62:38
$Sc(OTf)_3$	15:85
(tBuBox)$Cu(SbF_6)_2$	2:98[c]
(BIPHEP)$Pt(SbF_6)_2$[d]	83:17
(BINAP)$Pt(SbF_6)_2$[d]	100:0

[a] Reaction conditions **1**, 3 eq ethyl glyoxylate, 10 mol% catalyst, CH_2Cl_2, RT. [b] Determined by GC. [c] 81% *ee*
[d] Generated *in situi* from P_2PtCl_2 and $AgSbF_6$



(BINOL)$TiCl_2$ **[(tBuBox)Cu][SbF_6]$_2$** **[(BIPHEP)Pt][SbF_6]$_2$**
[(BINAP)Pt][SbF_6]$_2$

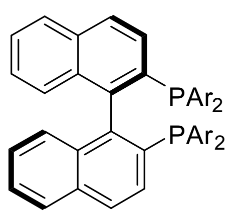
Figure 2.1 Structures of test catalysts for Prins cyclizations.

Because good facial control in additions to glyoxylate esters is well established for chiral P_2Pt^{2+} catalysts,[10] the likelihood of discovering a highly enantioselective variant of our catalyst was high. We therefore did an extensive examination of readily available chiral diphosphines. The results of the screening process (abbreviated list shown in Table 2.2) showed that ligands of the BINAP series were best for selectivity of the Prins reaction product **3** over the –ene product **2**. Additionally, BINAP and tol-BINAP also gave the highest enantioselectivitites, 60% (for one of two observed diastereomers) under these unoptimized reaction conditions.

Table 2.2. Representative screen of bisphosphine ligands for Pt^{2+} catalyzed Prins reaction [a]

P_2	3:2[b]	dr 3[b]	% *ee* of 3_1[b,c]
(*R*)-MeO-BIPHEP	83:17	1:1	39
(*R*)-p-tBu-MeO-BIPHEP	61:39	1:1.4	32
(*R*)-p-MeO-MeOBIPHEP	90:10	1.3:1	48
(*R*)-p-CF_3-MeO-BIPHEP	69:31	2:1	12
(*R*)-3,5-Me_2-MeO-BIPHEP	86:14	1.2:1	38
(R)-Cl-OMe-BIPHEP	86:14	1.3:1	58
(R)-BINAP	100:0	1.3:1	60
(R)-tol-BINAP	100:0	1:1	60
(R)-xylyl-BINAP	100:0	1.3:1	38
(R)-PHANEPHOS	88:11	3.6:1	0
(S,S)-CHIRAPHOS	30:70	1:1	0

[1]Reaction conditions: **1**, 3 eq. ethyl glyxoylate, 10% P_2PtCl_2, 20% $AgSbF_6$, 1:2 $ClCH_2CH_2Cl$:toluene, RT. [b] Determind by GC. [c] One (major) of two observed distereomers (*vida infra*).



Ar = Ph BINAP
Ar = 4-MePh tol-BINAP
Ar = 3,5-Me₂Ph xylyl-BINAP

Figure 2.2. Structures of BINAP type ligands.

10. (a) Ghosh, A. K.; Matsuda, M. *Org. Lett.* **1999**, *1,* 2157-2159. (b) Becker, J. J.; White, P. S.; Gagné, M. R. *J. Am. Chem. Soc.* **2001**, *123,* 9478-9479. (c) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3,* 1233-1236. (d) Pignat, K.; Vallotto, J.; Pinna, F.; Strukul, G. *Organometallics* **2000**, *19,* 5160-5167. (e) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2,* 4059-4062. (f) Oi, S.; Tereda, E.; Ohuchi, K; Kato, T.; Tachibana, Y.; Inoue, T. *J. Org. Chem.* **1999**, *64,* 8660-8662. (g) Oi, S.; Kashiwaga, K.; Inoue, Y. *Tetrahedron Lett.* **1998**, *39*, 6253-6256. (h) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.; Nieuwenhuyzen, M.; Rath, R. K. *Organometallics*, **2005**, *24*, 5945-5955.

The reaction conditions were further optimized by studying the effect of various solvents. It was noted that the enantioselectivity was solvent dependent, and increased with decreasing polarity (Table 2.3), perhaps suggesting a tighter transition state structure in the less polar solvents; donor solvents completely inhibit catalysis. Counterintuitive, however, was the shift from the Prins to the –ene product when the very polar nitromethane was used. This may suggest that a stabilizing interaction between the phenol trap and developing charge on the alkene is important for efficient trapping. This interaction is broken by solvation of the cation by very polar solvent leading to less efficient trapping; allowing the proton transfer of the step-wise –ene reaction to occur (see Scheme 2.2). This hypothesis is supported by the observation of less –ene product as the nitromethane is diluted with dichloromethane.

Table 2.3. Solvent Effects[a]

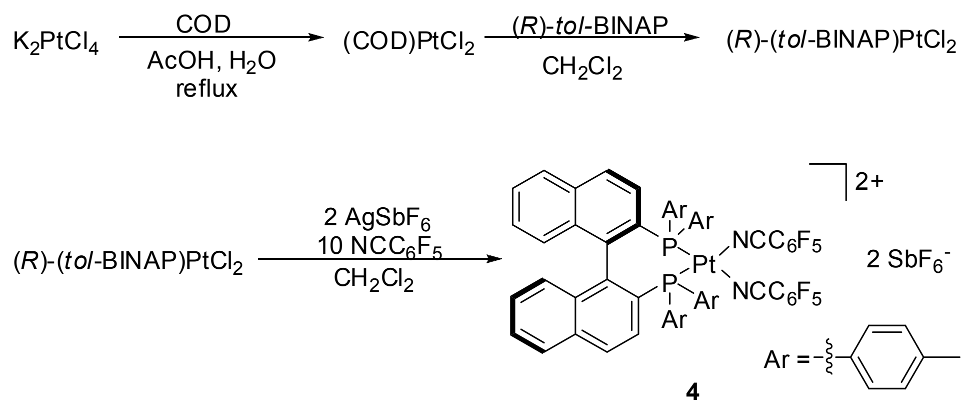
Solvent	ε[b]	3:2[c]	%ee 3_1[c,d]
CH_3NO_2	38.6	33:67	0
1:1 CH_3NO_2:CH_2CH_3	23.8	55:45	0
1:3 CH_3NO_2:CH_2Cl_2	16.3	83:17	18
CH_2ClCH_2Cl	10.4	100:0	22
CH_2Cl_2	8.9	100:0	30
PhCl	5.62	100:0	58
PhF	5.42	100:0	54
1:1 CH_2Cl_2:$PhCH_3$	5.64	100:0	56
1:2 CH_2Cl_2:$PhCH_3$	4.55	100:0	57
1:3 CH_2Cl_2:$PhCH_3$	4.01	100:0	66
1:7.5 CH_2Cl_2:$PhCH_3$	3.88	100:0	70

[a]Reaction conditions: **1,** 3 eq. ethyl glyoxylate, 10 mol% (*R*)-(BINAP)$PtCl_2$, 20% $AgSgF_6$, solvent, RT. [b] Mixed solvente systems dielectric calculated by weighted avergage. [c] Determined by GC. [d] One of two observed diastereomers (*vida infra*)

Because the least polar solvent system that our (BINAP)$PtCl_2$ catalyst precursor was soluble in was a 1:7.5 mixture of dichloromethane and toluene and the enantioselectivites increased with decreasing polarity it was desirable to synthesize an isolated dicationic catalyst that could be used directly in toluene and need not be activated with Ag(I) salts. We therefore isolated the (tol-BINAP)Pt^{2+} catalyst as its bis(pentafluorobenzonitrile) adduct

(**4**).[11] The complete synthesis of **4** starting from the commercial platinum source, K_2PtCl_4 is shown in Scheme 2.5. When 10 mol% **4** was used in the reaction of **1** with ethyl glyoxylate in toluene, **3** was generated in 85% yield as 1:1.2 mixture of diastereomers (78 and 48% *ee*, respectively).

Scheme 2.8



B. Scope and Limitations. To further improve the selectivity, we shifted our attention to the effect of the glyoxylate ester's size on enantioselectivity. Results (Table 2.4) showed that one diastereomer's *ee* was much more sensitive to the size of the glyoxylate ester (24 → 94%) than the other (74 → 96%), with R = tBu giving the best selectivities for both diastereomers.[12] Despite the sensitivity of the aldehyde's facial bias, the diastereofacial selectivity of the nucleophilic alkene was largely unaffected by the glyoxylate ester substitutent; efforts to improve the reaction dr's proved unsuccessful.

The optimum catalytic system was then applied to several classes of substrates (Table 2.5). Results showed that several phenols were capable reactants, and provided the Prins

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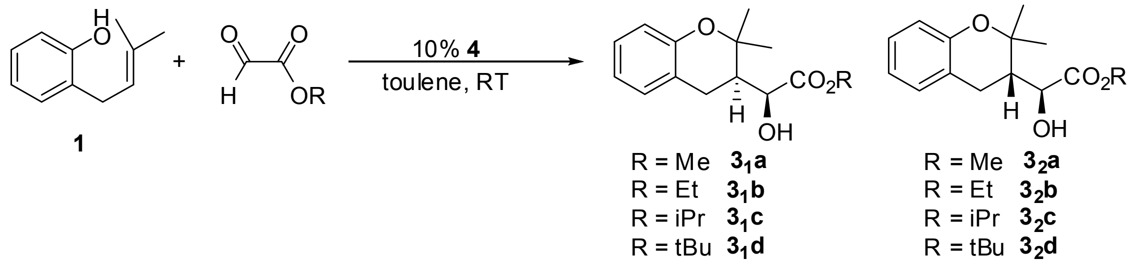
11. Becker, J. J.; Van Orden, L. J.; White, P. S.; Gagné, M. R. *Org. Lett.* **2002**, *4*, 727-730.

12. The relative stereochemistry was determined by nOe; absolute stereochemistry at the carbinol center was determined by Mosher's ester analysis. See experimental section.

Table 2.4. Effect of Glyoxylate Ester Size.[a]



R	**3:2**[b]	***dr*** **(3_1:3_2)**	**%*ee* 3**
Me	100:0	1:1.5[c]	74:24[b]
Et	100:0	1:1.2[b]	78:48[d]
iPr	100:0	1:1[b]	82:86[d]
tBu	100:0	1:1[b]	96:94[d]

[a] Reaction conditions: **1**, 3 eq. glyoxylate, 10 mol% **4**, toluene, RT. [b] Determined by GC. [c] Determined by ^{1}H NMR [d] Determined by SFC.

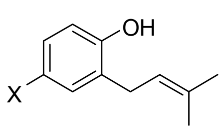
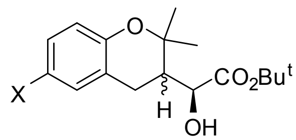
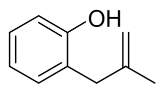
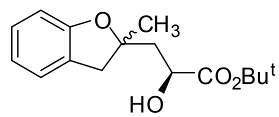
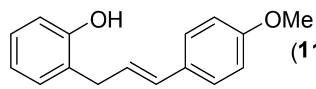
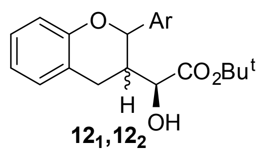
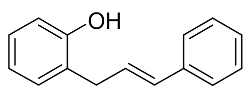
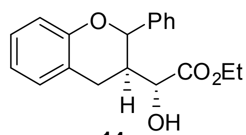
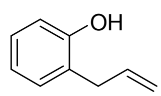
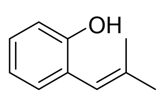
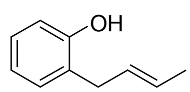
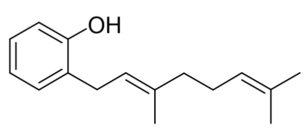
product cleanly and with good to excellent *ee*'s. The nucleophilicity of the phenol trap, varied by changing the substitutent para to the phenol, made little difference in the yield of the chroman. The exception to this was the tBu glyoxylate/**5** (entry 2) combination, which gave numerous unidentified products; ethyl glyoxylate/**5** (entry 3), however, was well behaved and gave products in the expected *ee* range.

A 1,1-disubstituted olefin was also tested (entry 5) and although the expected benzofuran Prins product was obtained, the yields were diminished because of competing –ene chemistry. Additionally, *p*-OMe styryl groups are competent nucleophiles providing the aryl substituted chroman in good yield and *ee* (entry 6).

The unsubstituted 2-cinnamyl phenol (**13**) (entry 7), however, was unreactive under the standard conditions, thus bracketing the nucleophilicity necessary for addition.[13] The insufficient nucleophilicity of the cinnamyl case could be compensated for by the addition of small amounts of Brønsted acid co-catalyst (0.05% HOTf). Although the acid sensitivity of

13. Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77.

Table 2.5. Asymmetric Prins Cyclizations

	Alkene		Glyoxylate	Product	dr	Yield[a]	%*ee*(1:2)[b]
1		X = H (**1**)	**tBu**	 X = H **3_1d, 3_2d**	1:1	76%	96:94
2		X = OMe (**5**)	**tBu**	X = OMe **6b,d_1, 6b,d_2**	---	---[d]	92:90
3			**Et**		1:1	60%	76:48
4		X = Cl (**7**)	**tBu**	X = Cl **8_1, 8_2**	1.9:1	72%	92:88
5		(**9**)	**tBu**	 **10_1,10_2**	1.2:1	42%	53:88
6		(**11**)	**tBu**	 **12_1,12_2**	1:1	81%	92:97
7[d]		(**13**)	**Et**	 **14** 7.5:1 d.r.	7.5:1	84%	68
8			**Et**	---	---	0%	---
9			**Et**	---	---	0%	---
10			**Et**	---	---	0%	---
11			**tBu**	Multiple Products	---	---	---

[a] Isolated. [b] enantioselectivities for the two diastereomers (see Experimental). [c] This substrate yielded only traces of product with tBu glyoxylate but reacted cleanly with ethyl glyoxylate. [d] with 0.05% added HOTf.

the *t*-butyl ester precluded the use of tBu glyoxylate, a successful and moderately diastereoselective (7.5:1) Prins reaction was achieved with **13** and ethyl glyoxylate.[14] We

14. The facial selectivity at the aldehyde is somehow reversed in this case, which provides **14** with the opposite absolute configuration at the carbinol center.

hypothesize that double activation[15] of the glyoxylate ester (H^+ and Pt^{2+}; see below) lowers the threshold nucleophilicity required for addition. The observation of moderate enantioselectivity (68%) precludes the possibility of pure Brønsted acid catalysis. Allyl, crotyl, and styrene nucleophiles were not competent (entries 8-10), even with added Brønsted acid, confirming the notion of a minimum alkene nucleophilicity for accessing cationic intermediates.[13]

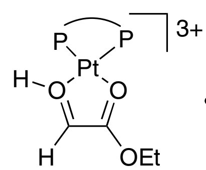


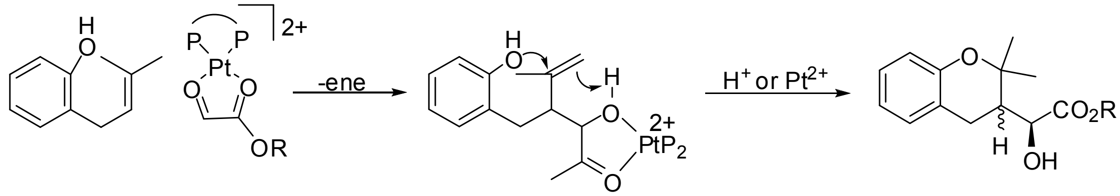
Figure 2.3. Proposed activation of glyoxylate by P_2Pt^{2+} and H^+.

Attempts at initiating a polycyclization with a dienol substrate (entry 11) were unsuccessful. The observation of numerous products suggested that there was little or no selectivity for which of the two substrate alkenes reacted even when bulky tBu glyoxylate was used. Combined with multiple diastereomers possible and competing –ene reactions made type of reaction unsuitable for polycyclization.

C. Mechanistic Considerations. Two reasonable possibilities exist for the observed reactivity. 1) P_2Pt^{2+}-Lewis acids efficiently accessed the ionic intermediate and established conditions for phenol trapping to be more rapid than proton transfer; and 2) that the reaction initially goes via a classic –ene pathway, but that the P_2Pt^{2+} additionally functions as a good Brønsted-Lewis Acid (eq. 2.3) to isomerize **2** to **3** (or that **2** is isomerized **3** by another mechanism under the reaction conditions). The fact that **2** is not observed during the reaction

15. For examples of double activation in carbonyl addition reactions, see: (a) Aspinall, H. C.; Bissett, J. S.; Greeves, N; Levin, D. *Tet. Lett.* **2002**, *43,* 319-321. (b) Vaugeois, J.; Simard, M.; Wuest, J. D. *Coord. Chem. Rev.* **1995**, *145,* 55-73. (c) Wuest, J. D. *Acc. Chem. Res.* **1999**, *32,* 81-89. (d) Gravel, M.; Lachance, H.; Lu, X.; Hall, D. G. *Synthesis* **2004**, 1290-1302.

catalyzed by **4** and that control experiments show that **2** is *not* converted to **3** under the reaction conditions, strongly suggest that case 1) is dominant.

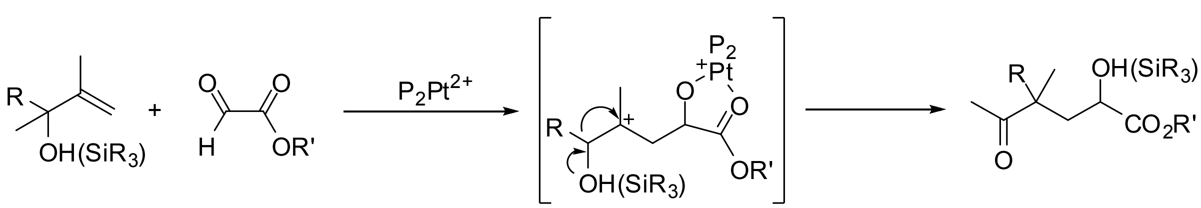


(2.3)

The observation of good enantioselectivity yet poor diastereoselectivity in these reactions is difficult to rationalize. From the data, it appears that a bulky glyoxylate -OR group works with the chiral diphosphine to create an environment with a good carbonyl facial bias, however, this arrangement communicates little diastereofacial selectivity onto the prochiral alkene nucleophiles.

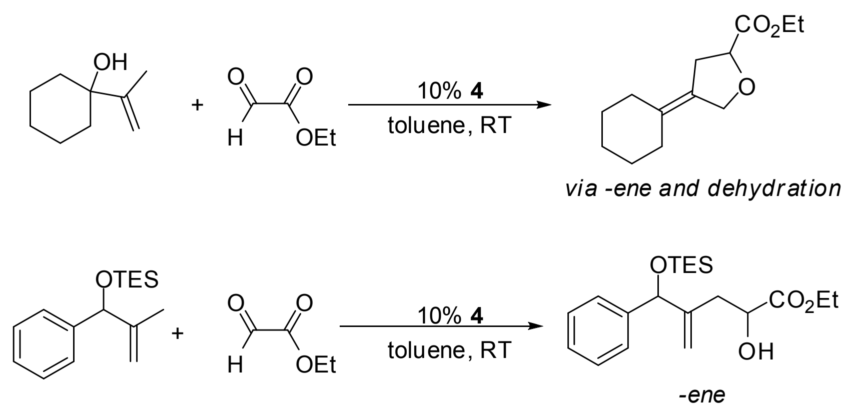
D. Carbocation Rearragments. The observation that the Prins cyclization trapping of a carbocation appeared to be unique to the use of P_2Pt^{2+} catalysts led us to investigate the possibility of using such a generated cation to initate a pinacol rearragment. Several allyl alcohol and allyl silyl ether substrates were prepared reasoning that the carbocation generated from nucleophilic attack of the alkene on the aldehyde could be quenched via a hydride or alkyl shift to generate the more stable oxocarbenium ion with transfer of H^+ (or R_3Si^+) to the aldehyde oxygen to generate a new carbonyl (Scheme 2.6). Unfortunately, most of the substrates gave products of –ene reactions or decomposed via dehydration of the allyl alcohol (examples in Scheme 2.7).

Scheme 2.9

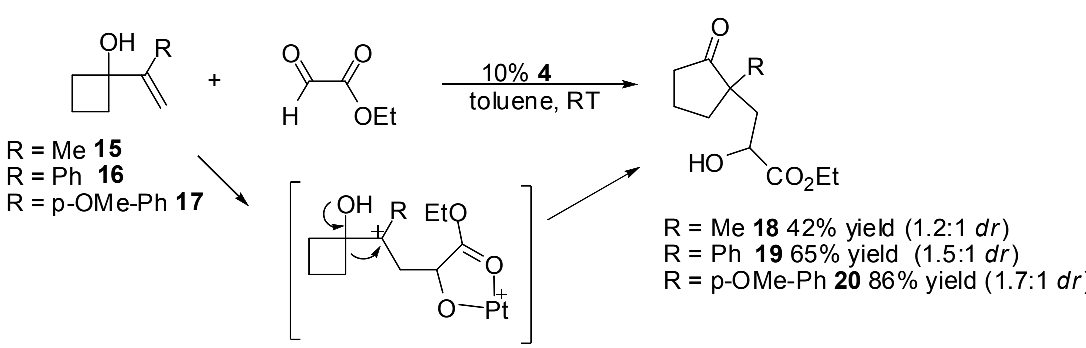


Reasoning that cations were in fact generated, but that the step-wise –ene proton transfer was a faster route than the desired pinacol rearrangement, we devised substrates that incorporated an element of ring strain, providing a driving force for ring-expanding pinacol rearragment. Allyl cyclobutanol substrates 15-17 were prepared with this notion in mind. Reaction with 3 eq. ethyl glyoxylate in the presence of 10% 4 led to the α-hydroxy ester substituted cyclopentanone products 18-20, as mixtures of diastereomers (Scheme 2.8). The yields of the cyclopentanone products increased with the ability of the alkene substituent to stabilize a cation.

Scheme 2. 10

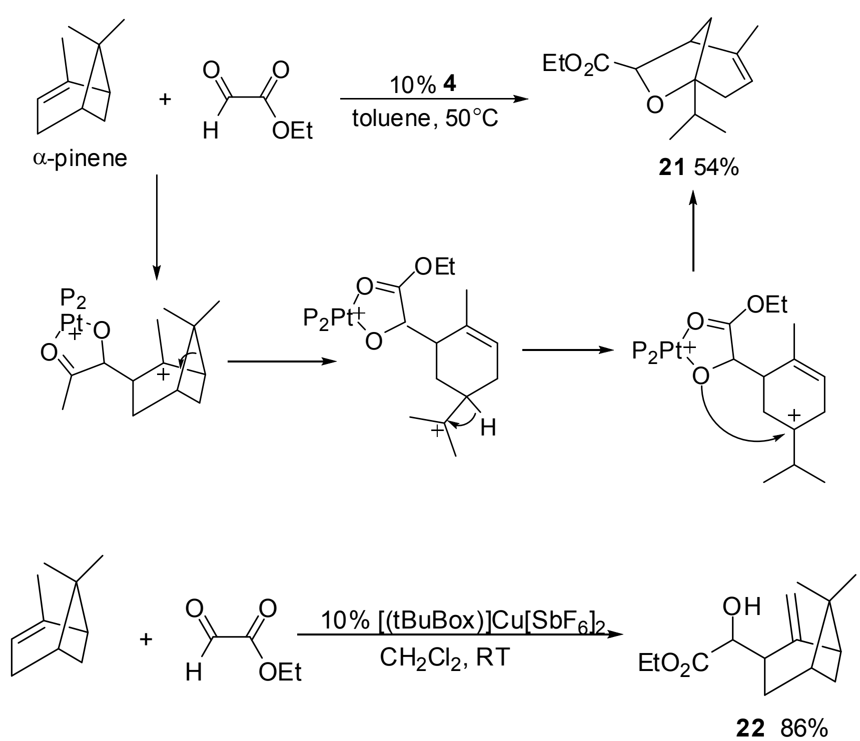


Scheme 2.11



Another example of the use of ring strain as a driving force for promoting the rearrangement of a carbocation is the use of the natural bicyclic product α-pinene as a substrate. The reaction of α-pinene and ethyl gyloxylate in the presence of 10% **4** yielded numerous isomeric products of the addition of α-pinene to ethyl glyoxylate. Optimization of the reaction conditions allowed isolation of the major product (**21**) in 54% yield. A plausable mechanism for the formation of **21** is given in Scheme 2.9 and includes key steps of cation generation, C-C shifting, ring expansion/contraction and cation trapping by a platinum alkoxide. Further supporting the notion that P_2Pt^{2+}s are unique in their ability to generate the products of carbocation generation is the observation that when the catalyst is changed in this reaction from **4** to [(tBu-Box)Cu][SbF_6]$_2$ the –ene reaction adduct **22** is obtained in 86% yield (Scheme 2.9). Since significant ring strain (i.e. chemical potential) is incorporated into this starting alkene, this reaction can be view as a sensitive probe for the generation of ionic species during the –ene reaction. As previously mentioned, despite computional evidence that (tBu-Box)Cu^{2+} catalyst mediate the –ene reaction via cationic intermediates, these charge sensitive substrates do not report in any charge build up at the key tertiary center.

Scheme 2.12



2.3 Conclusion

The first example of an asymmetric Prins reaction has been developed using P_2Pt^{2+} cataysts. For the reaction of alkenyl phenols with glyoxylate esters, excellent enantioselectivites were achieved using tol-BINAP as the chiral bis-phosphine ligand. This reaction was made possible because the highly Lewis acidic P_2Pt^{2+} catalysts were uniquely able to generate trappable carbocationic intermediates in analogy to the step-wise carbonyl–ene reaction pathway, while other Lewis acid catalysts gave the products of –ene ractions. Carbocation rearrangements were also possible, provided that strain relief was incorporated in the design of substrates to make the rearrangements faster than competing step-wise –ene proton transfer. Poor diastereoselectivity and lack of selectivity for nucleophilic alkenes made this method not useful for polycyclization. An α-pinene based method has also been developed for examining the degree of charge buildup during –ene type reactions. When charge buildup is significant then strain releasing C-C bond formation/breakage events occur.

2.4 Experimental

General Proceures:

Methyl glyoxylate was prepared according to a literature procedure[16] and freshly distilled from P_2O_5 prior to use. Ethyl glyoxylate was purchased from Lancaster and freshly distilled prior to use by the method of Evans.[17] Isopropyl glyoxylate and *tert*-butyl glyoxylate were prepared according to a literature procedure[16] and purified/cracked by the following method: 5 g glyoxylate was refluxed in 75 mL benzene in the presence of 2 mg pyridinium tosylate for 1 h. The benzene/water azeotrope and excess benzene were distilled off at a bath temperature of 95 °C. Then the bath temperature was raised to 115 ºC for 1 h. Distillation at reduced pressure yielded a mixture of glyoxylate and benzene the proportions of which could be measured by ^{1}H NMR (generally 50-70% glyoxylate). Substituted 2-allyl phenols (**1, 5, 7, 9,** and **11**)[18] and (cod)$PtCl_2$[19] were prepared according to literature procedures. (*R*)-tol-BINAP was purchased from Strem and used as received. Toluene and CH_2Cl_2 were passed though a column of alumina, and freeze-pump-thaw degassed prior to use. All other chemicals were purchased from Aldrich and used as received. All Prins cyclization reactions were performed under N_2 using standard Schlenk techniques. NMR chemical shifts are reported in ppm and referenced to residual solvent peaks (^{1}H and ^{13}C) or to an external standard (85% H_3PO_4, ^{31}P) ($CFCl_3$, ^{19}F). SFC was performed on a Berger Mini-Gram. GC

16. Kelley. T. R.; Schmidt, T. E.; Haggerty, J. G. *Synthesis*, **1972**, 544-545.

17. Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovosky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824-5825.

18. Yamad, S.; Ono, F.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jap.* **1977**, *50*, 750-755.

19. Drew, D.; Doyle, J. R. *Inorg. Syn.* **1990**, *28*, 346-349.

was performed on an HP-6890. Elemental analysis was preformed by Robertson Microlit Laboratories, Inc. (Madison, NJ).

(*R*)-[(tol-BINAP)Pt(NCC_6F_5)$_2$][SbF_6]$_2$ (4). To a stirring solution of 275.8 mg (0.737 mmol) of (cod)$PtCl_2$ in 20 mL of CH_2Cl_2 was added dropwise 500.0 mg (0.737 mmol) of (*R*)-tol-BINAP in 20 mL CH_2Cl_2. After 30 min of stirring the solvent was removed in *vacuo* and the yellow solid precipitated from CH_2Cl_2/hexanes to yield 602 mg (86% yield) of (*R*)-(tol-BINAP)$PtCl_2$ as a white powder. (*R*)-(tol-BINAP)$PtCl_2$ (560 mg, 0.593 mmol) and 448.3 mg (1.30 mmol) of $AgSbF_6$ were then taken up in 50 mL CH_2Cl_2 under N_2 in a flask protected from light. Pentafluorobenzonitrile (747 μL, 5.93 mmol) was added and the mixture was stirred for 3 h. The reaction mixture was opened to the atmosphere and filter through a 0.45 μm PTFE filter and the solvent removed in *vacuo*. The oily residue was then precipitated from CH_2Cl_2/hexanes to yield 925 mg (90% yield) of white powder. ^{31}P NMR (162 MHz, CD_2Cl_2) δ -0.4 (s, $J_{P\text{-}Pt}$ = 3719 Hz). ^{19}F NMR (376 MHz, CD_2Cl_2) δ -127.2 (2F), -135.6 (1F), -157.0 (2F). ^{1}H NMR (400 MHz, CD_2Cl_2) δ 7.76 (m, 7H), 7.70 (d, *J* = 8.4 Hz, 4H), 7.56 (m, 5H), 7.46 (d, *J* = 7.6 Hz, 5H), 7.25 (t, *J* = 8.0 Hz, 3H), 6.75 (d, *J* = 8.8 Hz, 4H), 2.40 (s, 6H), 2.01 (s, 6H). ^{13}C{^{1}H, ^{31}P} NMR (76 MHz, CD_2Cl_2) δ 144.6, 143.6, 139.7, 135.3, 134.9, 134.8, 129.9, 130.3, 130.1, 128.5, 127.3, 122.0, 120.6, 114.5, 112.1, 21.4, 21.3. Anal. Calcd. for $C_{62}H_{40}F_{22}N_2P_2PtSb_2$: C, 43.01; H, 2.33, N 1.62. Found: C, 43.05, H, 2.45, N, 1.77.

Prins Cyclizations:

General: To a stirring suspension of **4** (69.4 mg, 0.040 mmol) in 2 mL toluene was added 1.2 mmol glyoxylate (prepared according to procedure described in general procedures). After 30 min of stirring the now homogeneous solution was transferred via syringe into another flask under N_2 containing 0.40 mmol substrate (**1, 5, 7, 19, 11** or **13**) and 40 μL of a 0.05 M solution of 2,6-ditertbutyl-4-methyl pyridine (0.002 mmol) in CH_2Cl_2. In the case of **11** the 2,6-ditertbutyl-4-methyl pyridine was replaced with 4 μL of a 0.05 M solution of HOTf (0.0002 mmol) in CH_2Cl_2. This solution was stirred overnight. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel.

Repeated chromatography was sometimes necessary to separate diastereomers. Unless otherwise noted, yields are reported for mixtures of diastereomers and NMR data is for diastereo-pure materials.

Methyl 2-(2,2-dimethylchroman-3-yl)-2-hydroxyacetate (3a): 81 mg, 81% yield. Anal. Calcd. for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.16; H 7.26. **3_1a.** Enantiomeric excess determined by GC t_R 49.3 (major); t_R 53.6 (minor) [SupelCo, β-dex 120(30 M x 0.25 mm), H_2, 150°C, 20 psi) as 74%. $[\alpha]^{25}$ = -15.32 (*c* 0.50, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 7.2 Hz, 1H), 6.79 (m, 2H), 4.52 (dd, *J* = 4.8, 1.6 Hz, 1H), 3.81 (s, 3H), 2.92 (dd, *J* = 17.6, 13.6 Hz, 1H), 2.87 (d, *J* = 4.8 Hz, 1H), 2.27 (m, 2H), 1.54 (s, 3H), 1.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.3, 153.2, 129.4, 127.4, 121.1, 120.0, 117.2, 77.2, 69.8, 53.1, 44.0, 27.6, 21.9, 21.6. **3_2a.** Enantiomeric excess determined by GC t_R 56.8 (major); t_R 57.9 (minor) [SupelCo, β-dex 120(30 M x 0.25 mm), H_2, 150°C, 20 psi) as 24%. $[\alpha]^{25}$ = +3.21 (*c* 0.50, MeOH). ^{1}H NMR(400 MHz, $CDCl_3$): δ 7.05 (m, 2H), 6.81 (dt *J* = 7.2, 1.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.25 (t, *J* = 3.2 Hz, 1H), 3.73 (s, 3H), 2.94 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.84 (d, *J* = 6.0 Hz, 1H), 2.70 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.35 (m, 1H), 1.40 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 153.5, 129.9, 127.1, 120.7, 120.1, 117.0, 72.3, 70.3 52.4, 44.7, 27.4, 26.7, 22.4.

Ethyl 2-(2,2-dimethylchroman-3-yl)-2-hydroxyacetate (3b). 90 mg, 85% yield. Anal. Calcd. for $C_{15}H_{20}O_4$: C, 68.16; H, 7.36. Found: C, 68.16; H, 7.73. **3_1b.** Enantiomeric excess determined by SFC (220 nm, 35 ºC): t_R 8.1 min (major); t_R 7.5 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 78% *ee*. $[\alpha]^{25}$ = -20.91 (*c* 0.35, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 6.8 Hz, 1H), 6.81 (t, *J* = 7.6 Hz, 1H), 6.78 (d, *J* = 8.4 Hz, 1H), 4.49 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.25 (m, 2H), 2.26 (m, 2H), 2.92 (m, 2H), 2.28 (m, 2H), 1.54 (s, 3H), 1.29 (s, 3H), 1.28 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 153.3, 129.4, 127.3, 121.2, 119.9, 117.2, 69.7, 62.4, 44.0, 27.6, 21.8, 22.6, 14.6. **3_2b.** Enantiomeric excess determined by SFC (220 nm, 35 ºC): t_R 12.1 min (major); t_R 11.3 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 44% *ee*. $[\alpha]^{25}$ = +16.62 (*c* 0.60, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (m, 2H), 6.81 (dt *J* = 7.2, 1.2 Hz, 1H), 6.75 (d, *J* = 8.4 Hz, 1H), 4.20 (m, 3H), 2.94 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.84 (d, *J* = 6.0 Hz, 1H), 2.70 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.35 (m, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.30 (t, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 153.2, 129.2, 127.4, 120.9, 120.0, 117.0, 72.3, 62.0, 44.7, 27.8, 26.6, 22.2, 14.0.

Isopropyl 2-(2,2-dimethylchroman-3-yl)-2-hydroxyacetate (3c): 90 mg, 81% yield. Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found C, 69.14; H, 7.87. **3_1c**: Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 9.0 min (major); t_R 7.7 min (minor) [Chiracel OD-H (0.46 cm x 25) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 82% *ee*. $[\alpha]^{25}$ = -30.7 (*c* 0.50, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.07 (t, *J* = 8.0 Hz, 1H), 7.02 (d, *J* = 7.6 Hz, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 5.11 (septet, *J* = 6.4 Hz, 1H), 4.43 (d, *J* = 4.8 Hz, 1H), 2.92 (m, 2H), 2.26 (m, 2H), 1.55 (s, 3H), 1.29 (s, 3H), 1.27 (d, *J* = 6.4 Hz, 3H), 1.24 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ174.4, 153.4, 129.4, 127.3, 121.3, 120.0, 117.2, 76.8, 70.4, 69.8, 44.1, 27.7, 21.8, 21.7, 21.7, 21.6. **3_2d.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 14.6 min (major); t_R 14.0 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 86% *ee*. $[\alpha]^{25}$ = +14.84 (*c* 0.38, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.81 (dt, *J* = 7.6, 1.2 Hz, 1H), 6.75 (dd, *J* = 8.0, 0.8 Hz, 1H), 5.08 (septet, *J* = 6.0 Hz, 1H), 4.15 (dd, *J* = 5.2, 4.0 Hz, 1H), 2.95 (dd, *J* = 16.8 Hz, 12.0 Hz, 1H), 2.83 (d, *J* = 4.0 Hz, 1H), 2.67 (dd, *J* = 16.4, 5.2 Hz, 1H), 2.36 (ddd, *J* = 12.0, 5.2, 4.0, 1H), 1.41 (s, 3H), 1.30 (s, 3H), 1.29 (d, *J* = 6.4 Hz, 3H), 1.27 (d, *J* = 6.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.2, 153.2, 129.2, 127.4, 121.1, 120.0, 117.0, 76.7, 72.6, 70.3, 44.6, 27.9, 27.0, 21.2, 21.8, 21.6.

Tert-butyl 2-(2,2-dimethylchroman-3-yl)-2-hydroxyacetate (3d): 89 mg, 76% yield. Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.08; H, 7.98. **3_1d.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 7.6 min (major); t_R 6.7 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 96% *ee*. $[\alpha]^{25}$ = -30.7 (*c* 0.50, MeOH). ^{1}H NMR (400 MHz, CDCl3) δ 7.07 (t, *J* = 8.7 Hz, 1H), 7.03 (d, *J* = 7.6 Hz, 1H), 6.81 (t, *J* = 8.4Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 4.8, 2.0 Hz, 1H), 2.91 (m, 2H), 2.25 (m, 2H), 1.54 (s, 3H), 1.47 (s, 9H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ174.0, 153.3, 129.5, 127.2, 121.4, 119.9, 117.2, 83.3, 70.0, 44.1, 28.0, 27.7, 21.5. **3_2d.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 13.5 min (major); t_R 12.6 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 94% *ee*. $[\alpha]^{25}$ = +14.84 (*c* 0.38, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (t, *J* = 7.2 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.82 (t, *J* = 8.4 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.01 (t, *J* = 4.0 Hz, 1H), 2.96 (dd, *J* = 16.8, 12.0 Hz, 1H), 2.88 (d, *J* = 5.2 Hz, 1H), 2.70 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.32 (ddd, *J* = 11.6, 5.2, 3.6 Hz, 1H), 1.47 (s, 9H), 1.42 (s, 3H), 1.30 (s, 3H). ^{13}C NMR

(100 MHz, $CDCl_3$) δ173.9, 153.3, 129.2, 127.4, 121.2, 120.0, 117.0, 83.4, 72.8, 44.6, 28.0, 27.9, 27.1, 22.3.

Ethyl 2-hydroxy-2-(6-methoxy-2,2-dimethylchroman-3-yl)acetate (6b): 71 mg, 60% yield. Anal. Calcd. for $C_{18}H_{26}O_5$: C, 67.06; H, 8.13. Found: C, 65.45; H, 7.63. **6_1b.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 9.7 min (major); t_R 10.4 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 76% *ee*. $[\alpha]^{25}$ = -32.5 (*c* 0.50, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (m, 2H), 6.57 (d, *J* = 2.8 Hz, 1H), 4.47 (dd, *J* = 4.8, 1.6 Hz, 1H), 4.26 (m, 1H), 3.72 (s, 3H), 2.89 (m, 2H), 2.26 (m, 2H), 1.52 (s, 3H), 1.29 (s, 3H), 1.28 (t, *J* = 6.4 Hz. 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9, 153.1, 147.2, 121.8, 117.7, 113.9, 113.5, 76.6, 69.7, 62.4, 55.7, 44.0, 27.6, 22.2, 21.5, 14.2. **6_2b.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 14.5 min (major); t_R 18.6 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1.5 mL/min] as 44% *ee*. $[\alpha]^{25}$ = +18.6 (*c* 0.45, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67(m, 2H), 6.57 (s, 1H), 4.20(m, 3H), 3.72 (s, 3H), 2.92 (dd, *J* = 16.8, 11.6 Hz, 1H), 2.83 (d, *J* = 5.6 Hz, 1H), 2.35 (m, 1H), 1.38 (s, 3H), 1.29 (s, 3H), 1.28 (t, *J* = 4.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.7, 153.1, 147.1, 121.5, 117.6, 113.6, 113.5, 76.4, 72.3, 62.0, 55.7, 44.6, 27.7, 27.0, 22.2, 14.0.

***Tert*-butyl 2-(6-chloro-2,2-dimethylchroman-3-yl)-2-hydroxyacetate (8d):** 94 mg, 72% yield**.** Anal. Calcd. for C17H23ClO4: C, 62.48; H, 7.09. Found: C, 62.76; H, 7.10. **8_1d:** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 8.4 min (major); t_R 7.9 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5/1.5, 1.5 mL/min] as 92% *ee*. $[\alpha]^{25}$ = -44.7 (*c* 0.60, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (m, 2H), 6.69 (d, *J* = 8.0 Hz, 1H), 4.33 (dd, *J* = 4.4, 1.6 Hz), 2.95 (d, *J* = 4.8 Hz, 1H), 2.87 (dd, *J* = 18.0, 14.0 Hz, 1H), 2.21 (m, 1H), 1.52 (s, 3H), 1.48 (s, 9H), 1.34 (s, 3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 173.8, 151.9, 129.0, 127.3, 124.6, 123.0, 118.5, 83.5, 69.5, 43.8, 28.0, 27.9, 27.5, 21.5. **8_2d:** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 13.3 min (major); t_R 14.0 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5:1.5, 1.5 mL/min] as 88% *ee*. $[\alpha]^{25}$ = +19.1 (*c* 0.20, MeOH). ^{1}H NMR (400 MHz,$CDCl_3$) δ 7.02 (m, 2H), 6.80 (d, *J* = 6.8 Hz, 1H), 4.06 (d, *J* = 3.6 Hz), 2.92 (m, 2H), 2.67 (dd, *J* = 16.8, 5.6 Hz), 2.29 (m, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.34 (s,3H). ^{13}C NMR (100MHz, $CDCl_3$) δ 173.7, 151.9, 128.7, 127.4, 124.6, 122.8, 118.4, 83.9, 72.6, 44.2, 28.3, 27.9, 27.0, 22.3.

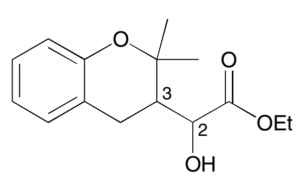
***Tert*-butyl 2-hydroxy-3-(2-methyl-2,3-dihydrobenzofuran-2-yl)propanoate (10):** 46.8 mg, 42% yield as an inseparable mixture of diastereomers. Enantiomeric excesses determined by GC: t_R 58.6 min (diastereomer 1, major); t_R 59.9 min (diastereomer 1, minor); t_R 62.2 min (diastereomer 2, major); t_R 64.7 min (diastereomer 2, minor) [SupelCo, β-dex 120 (30M x 0.25mm), H_2, 145°C, 20 psi) as 53% and 88% *ee*, respectively. ^{1}H NMR (400MHz, $CDCl_3$) δ 7.10 (m, 2H), 6.81 (m, 1H), 6.72 (t, *J* = 8.0 Hz, 1H), 4.26 (m, 1H), 3.38 (d, *J* = 15.6 Hz, 0.5H), 3.31 (d, *J* = 16.0 Hz, 0.5H), 3.10 (d, *J* = 6.0Hz, 0.5H), 3.08 (d, *J* = 4.4 Hz, 0.5H), 2.97 (d, *J* = 16.0 Hz, 0.5H), 2.95 (d, *J* = 16.0 Hz, 0.5H), 2.33 (m, 1H), 1.99 (m, 1H), 1.50 (s, 1.5H), 1.49 (s, 1.5H), 1.46 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 174.0, 158.4, 158.3, 128.0, 127.9, 127.1, 125.1, 120.2, 120.2, 116.8, 87.9, 87.8, 68.4, 44.5, 44.4, 42.4, 41.4, 28.1, 28.0, 27.0, 26.2. Anal. Calcd. for $C_{16}H_{24}O_4$: C, 69.04, H, 7.97. Found: C, 68.76, H, 7.88.

***Tert*-butyl 2-hydroxy-2-(2-(4-methoxyphenyl)chroman-3-yl)acetate (12):** 20 mg, 81% yield. Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33 H, 7.07. Found: C, 70.97, H, 7.42. **12_1.** Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 31 min (minor); t_R 39 min (major) [Chiracel AD-H (0.46 cm x 25 cm) CO_2/MeOH 97/3, 1 mL/min] as 97% *ee*. $[\alpha]^{25}$ = -11.9 (*c* 1.1, MeOH). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.4 Hz, 2H), δ7.11 (m, 2H), 6.95 (d, *J* = 8.4 Hz, 2H), 6.88 (m, 2H), 4.90 (d, *J* = 9.6 Hz, 1H), 3.83 (s, 3H), 3.75 (dd, *J* = 4.4, 2.4 Hz, 1H), 3.10 (dd, *J* = 13.6, 4.0 Hz, 1H), 2.87 (d, *J* = 4.4 Hz, 1H), 2.42 (m, 2H), 1.45 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6, 159.7, 154.9, 131.0, 129.7, 128.7, 127.3, 121.5, 120.5, 116.8, 114.1, 83.2, 79.4, 69.4, 55.4, 41.6, 28.0. **12_2**. Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 48 min (major); t_R 62 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 98.5/1.5, 1.5 mL/min] as 92% *ee*. $[\alpha]^{25}$ = +10.7 (*c* 0.9, MeOH). ^{1}H NMR (400MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.4 Hz, 2H), 7.09 (m, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 6.82 (m, 2H), 5.08 (d, *J* = 9.2 Hz), 3.90 (dd, *J* = 6.8 Hz, 3.6 Hz,1H), 3.00 (d, *J* = 4.0 Hz, 1H), 2.96 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.77 (dd, *J* = 16.0, 4.8 Hz, 1H), 2.61 (m, 1H), 1.45 (s, 9H). ^{13}C NMR (100MHz, $CDCl_3$) δ 172.8, 159.7, 154.7, 131.3, 129.4, 128.8, 127.5, 121.2, 120.4, 116.6, 113.8, 83.6, 78.6,1.3, 55.3, 42.6, 28.1.

Ethyl 2-hydroxy-2-(2-phenylchroman-3-yl)acetate (14): 114mg, 84% yield. Enantiomeric excess determined by SFC (220 nm, 35º C): t_R 32.6 min (major); t_R 27.9 min (minor) [Chiracel OD-H (0.46 cm x 25 cm) CO_2/MeOH 96/4, 1 mL/min] as 68% *ee*. $[\alpha]^{25}$ = -32.7 (*c* 0.65, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (m, 2H), 7.36 (m, 3H), 7.10 (d, *J* = 7.6 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 2H), 5.11 (d, *J* = 9.2 Hz, 1H), 4.01 (t, *J* = 3.2 Hz, 1H), 3.96 (m, 1H), 3.79 (m, 1H), 3.03 (dd, *J* = 16.4, 11.2 Hz, 1H), 2.92 (m, 2H), 2.75 (m, 1H), 1.24 (t, 5.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 154.7, 139.0, 129.4, 128.6, 128.3, 127.9, 127.5, 121.4, 120.5, 116.6, 78.7, 71.4, 61.9, 42.0, 28.4, 13.9. Anal. Calcd. for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45 Found: C, 72.92; H, 6.27.

Determination of Stereochemistry for 3a-d, 6b, 8d.:

To assign the relative stereochemistry of products **3a-d**, **7b**, and **9d**, we carefully analyzed the stereoisomers of **3a** and then assigned the remainder by analogy. To begin, the structures of the lowest energy conformers/rotomers were computed using Monte-Carlo methods (AM1, MacSpartan 04). These structure(s) were then used to predict nOes. (Figure S1). They were then compared with experimental nOes for each isolated diastereomer of **3b** and **3d**, and assigned on the basis of the key differentiating nOes shown in Figure 2.1. The relative stereochemistry of the **3a,c-d, 7b,** and **9d** were assigned by analogy. Supporting a "by analogy" assignment, were relative chromatographic retention times of the diastereomers (SFC, GC, and tlc), characteristic upfield shift of the faster eluting isomer's carbinol hydrogen resonance (^{1}H NMR), and the sign of the optical rotation (Table 2.6). The faster eluting diastereomer was arbitrarily given the subscript **1** while the slower was given the subscript **2**. These data, in combination with Mosher's ester analysis[20] to determine the absolute stereochemistry of the carbinol center, allowed the assignment of diastereomer #$_{\mathbf{1}}$ as having the *S* configuration at the ring junction (C3) and the *S* configuration at the carbinol center (C2); diastereomer #$_{\mathbf{2}}$ was assigned the (3*R*,2*S*) stereochemistry.



20. Seco, J. M.; Quiñoá, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17-117.

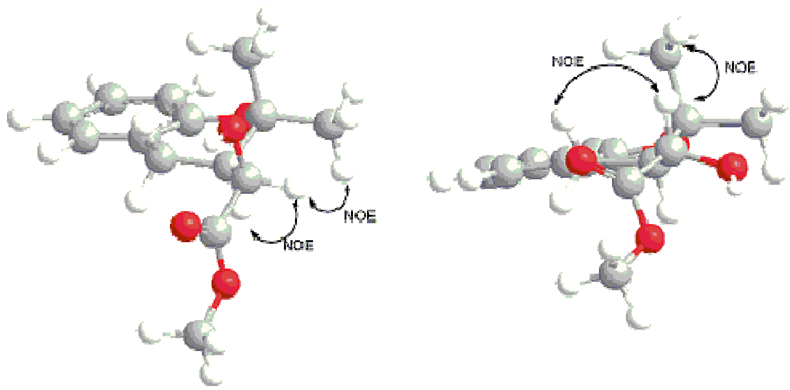


Figure 2.3 Key nOes predicted and observed for **3a-d**, **6b**, and **8**. Diastereomer **#$_1$** (left) and diastereomer **#$_2$** (right).

Table 2.6. Signs of optical rotations for enantioenriched Prins cyclization products.

	δ carbinol #$_1$	Rotation #$_1$	δ carbinol $_2$	Rotation #$_2$
3a	4.51	-	4.23	+
3b	4.35	-	4.22	+
3c	4.43	-	4.15	+
3d	4.35	-	4.07	+
7b	4.48	-	4.20	+
9d	4.33	-	4.05	+

Determination of stereochemistry for 13 and 15.

To assign the relative stereochemistry of products **13** and **15**, we carefully analyzed the stereoisomers of **15.** The relative stereochemistry between the ring stereocenters 3 and 4 was determined to be *trans* by the H-H coupling observed in the ^{1}H NMR (see characterization data) for all products of this type. The structures of the lowest energy conformers/rotomers were computed using Monte-Carlo methods (AM1, MacSpartan 04). These structure(s) were then used to predict nOes. (Figure S2). They were then compared with experimental nOes for each isolated diastereomer of **13** and **15**, and assigned on the basis of the key differentiating nOes shown in Figure 2.2. These data, in combination with Mosher's ester analysis[20] to determine the absolute stereochemistry of the carbinol center, allowed the assignment of **15**$_1$**.** These data, in combination with Mosher's ester analysis to determine the absolute stereochemistry of the carbinol center, allowed the assignment of **13**$_1$ as (4*R*,3*S*,2*S*), **13**$_2$ as (4*S*,3*R*,2*S*) and **15** as (4*R*,3*S*,2*R*).

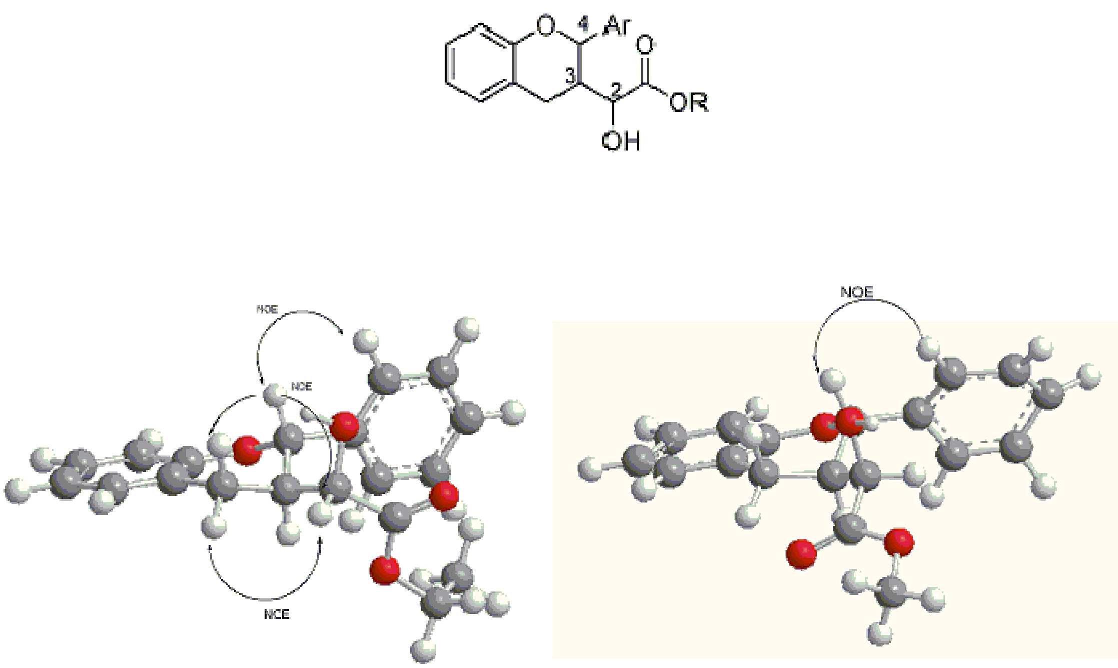


Figure 2.5: Key nOes predicted and observed for **13** and **15**. Diastereomer #$_1$ (left) and diastereomer #$_2$ (right).

Carbocation Rearrangements:

Substrate Synthesis: Cyclobutanol substrates **15-17** were prepared by addition of the apprioate Grignard reagent to cyclobutanone.

1-(prop-1-en-2-yl)cyclobutanol (15): Isopropenyl magnesium bromide (31.4 mL, 15.6 mmol) was added to a solution of 1.0 g cyclobutanone (14.2 mmol) in 30 mL diethyl ether at 0 °C and stirred at 0 °C for 3h. The reaction was quenched with 15% aqueous NH_4Cl and extracted with diethyl ether (3 x 30 mL). The organic portions were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by flash chromotography on silica gel eluted with 1:5 EtOAc:hexanes to yield 1.4 g (89% yield) of a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 5.31 (d, J = 8.8 Hz, 2H), 2.49 (m, 2H), 2.23 (m, 2H), 1.96 (m, 1H), 1.74 (s, 3H), 1.62 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.5, 111.9, 75.2, 39.9, 27.6, 18.3.

1-(1-phenylvinyl)cyclobutanol (16): 1,2-Dibromoethane (2.0 mmol, 0.2 mL) was added to a suspension of Mg turnings (40.0 mmol, 0.972 g) in THF (20 mL). After 10 min., 2.6 mL α-bromostyrene (20.0 mmol) in 5 mL THF was added dropwise, and the solution was heated to reflux for 2 h. The reaction was then cooled to 0°C and added via cannula filter to a solution of cyclobutanone (10.0 mmol, 0.8 mL) in 20 mL THF. The solution was allowed to stir at this temperature for 1 h and then the reaction was quenched with 15% aqueous NH_4Cl, and extracted with diethyl ether (3 x 30 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by flash chromatography eluted with 9:1 EtOAc:hexanes to yield 1.7g (53%) of a colorless oil. ^1H NMR (400 MHz, $CDCl_3$): δ 7.50 (m, 1H), 7.31 (m, 4H), 5.37 (d, J = 8.4 Hz, 2H), 2.49 (m, 2H), 2.26 (m, 2H), 2.00 (m, 1H), 1.93 (s, 1H), 1.63 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.2, 138.6, 128.8, 127.9, 126.7, 114.3, 86.2, 39.7, 39.4, 14.7.

1-(1-(4-methoxyphenyl)vinyl)cyclobutanol (17): Synthesized via a procedure similar to that for **16** using 1-(1-bromovinyl)-4-methoxybenzene.[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 9.6 Hz, 2H), 6.86 (d, *J* = 9.6 Hz, 2H), 5.33 (d, *J* = 1.6 Hz, 1H), 5.28 (d, *J* = 1.6 Hz, 1H), 3.82 (s, 3H), 2.46 (m, 1H), 2.28 (m, 2H), 1.96 (m, 1H), 1.62 (m, 1H), 1.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.1, 174.5, 159.1, 151.7, 128.7, 127.3, 113.5, 111.4, 78.1, 55.2, 35.7, 13.9.

General Procedure for Prins-pinacol: To a solution of **4** (69.4 mg, 0.04 mmol) in 2 mL CH_2Cl_2 was added 1.2 mmol freshly distilled ethyl glyoxylate. After 30 min of stirring the solution was transferred via syringe into another flask under N_2 containing 0.40 mmol substrate (**15, 16,** or **17**) and 40 μL of a 0.05 M solution of 2,6-ditertbutyl-4-methyl pyridine (0.002 mmol) in CH_2Cl_2. This solution was stirred for 6 h The solvent was removed *in vacuo* and the residue was purified by flash chromatography on silica gel eluting with 9:1 hexanes:EtOAc.

Ethyl 2-hydroxy-3-(1-methyl-2-oxocyclopentyl)propanoate (18): 36 mg (42% yield) as an inseparable mixture of diastereomers (1.2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.12 (q, *J* = 7.2 Hz, 2H), 3.98 (m, 0.5H), 3.80 (m, 0.5H), 2.20 (m, 8H), 1.33 (s, 1.5 H), 1.32 (s, 1.5 H), 1.29 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 220.3, 219.2, 69.7, 69.4, 57.5, 56.8, 46.7, 46.3, 43.1, 42.5, 37.0, 36.2, 33.9, 32.6, 31.0, 29.7, 20.7, 19.2, 18.7, 18.6, 14.2, 14.0.

Ethyl 2-hydroxy-3-(2-oxo-1-phenylcyclopentyl)propanoate (19): 72 mg (65% yield) as an inseparable mixture of diastereomers (1.5:1 dr). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43

21. Rappoport, Z; Gal, A. *J. Chem. Soc. Perkin Trans. II*, **1973**, 301-310.

(d, J = 6.4 Hz, 2H), 7.33 (m, 2H), 7.23 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.97 (m, 0.5 H), 3.80 (m, 0.5 H), 2.91 (m, 0.5H), 2.66 (m, 1H), 2.60 (d, J = 6.4 Hz, 1H), 2.51 (dd, J = 14.4, 2.8 Hz, 1H), 2.25 (m, 6H), 2.13 (m, 2H), 1.93 (m, 2H), 1.83(dd, J = 14.4, 11.2 Hz, 1H), 1.73 (m, 1H), 1.21 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 220.7, 219.1, 175.1, 174.3, 138.6, 137.8, 128.8, 128.7, 127.1, 127.2, 126.6, 126.4, 68.9, 68.2, 61.7, 61.4, 56.9, 56.0, 43.1, 42.2, 37.1, 36.4, 33.9, 33.9, 18.7, 18.7, 14.1, 14.0.

Ethyl 2-hydroxy-3-(1-(4-methoxyphenyl)-2-oxocyclopentyl)propanoate (20): 105 mg (86% yield) as two separate diastereomers (1.7:1). **20_1**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.12 (d, J = 7.2 Hz, 2H), 3.86 (m, 1H) 3.82 (s, 3H), 2.61 (m, 1H), 2.45 (m, 1H), 2.25 (m, 1H), 2.09 (m, 1H), 2.01 (m, 1H), 1.90 (m, 1H), 1.79 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 219.3, 175.3, 158.7, 128.5, 128.3, 114.2, 68.2, 61.8, 55.3, 55.2, 43.0, 36.2, 34.1, 18.7, 14.1. **20_2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.25 (d, J = 8.4 Hz, 2H), 6.89 (d, J = 8.4 Hz, 2H), 4.12 (m, 1H), 4.02 (m, 1H), 3.80 (s, 3H), 3.74 (m, 1H), 2.66 (m, 1H), 2.10 – 2.45 (m, 5H), 1.95 (m, 1H), 1.74 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 221.1, 175.3, 158.8, 129.8, 128.1, 114.2, 68.8, 61.4, 56.3, 55.2, 42.1, 37.0, 35.9, 18.7, 14.0.

Ethyl 5-isopropyl-2-methyl-6-oxabicyclo[3.2.1]oct-2-ene-7-carboxylate (21): To a solution of **4** (69.4 mg, 0.04 mmol) in 2 mL toluene was added 1.2 mmol freshly distilled ethyl glyoxylate. After 30 min of stirring the solution was transferred via syringe into another flask under N_2 containing 63.3 μL α-pinene (54.4 mg, 0.40 mmol). This solution was stirred for 4 h at 50 °C. The solvent was removed *in vacuo* and the residue purified by flash chromatography on silica gel eluting with 19:1 hexanes:EtOAc to yield 51 mg of a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (s, 1H), 4.38 (s, 1H), 4.15 (m, 2H), 2.57

(d, J = 4.4 Hz, 1H), 2.20 (m, 1H), 2.07 (m, 1H), 2.00 (dd, J = 14.0, 6.8 Hz, 1H), 1.81 (ddd, J = 10.8, 4.4, 1.2 Hz, 1H), 1.76 (m, 3H), 1.65 (d, J = 10.8 Hz, 1H), 1.54 (s, 3H), 1.25 (t, J = 5.2 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.9, 135.7, 123.3, 91.4, 83.9, 61.6, 52.9, 35.4, 34.8, 33.2, 21.0, 17.8, 14.1.

Chapter 3

Oxidative Cation-Olefin Polycyclization

3.1 Introduction

Biomimetic polyolefin cascade reactions are among the most challenging problems in reaction design; however, because large increases in molecular complexity can be obtained in a single step, chemists have strived to develop synthetic methodologies analogous to enzymatic processes.[1,2] Methodologies previously employed include ionization of epoxides and acetals with Lewis acids,[3] protonation of alkenes with Brønsted acids,[4] and addition of mercuric salts to olefins.[5]

Recently, the reach of synthetic polycyclization reactions has been expanded to allow for asymmetric variation. Yamomoto has developed chiral Brønsted-Lewis Acid (BLAs)

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1. For a discussion on biosynthesis of terpenoid natural products see Chapter 1.

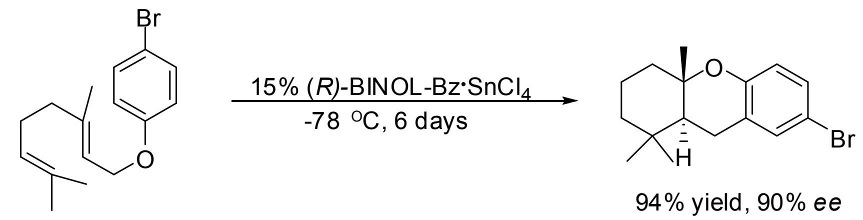
2. (a) Bartlet, P. A. in *Asymmetric Synthesis*; Morrison, J.D.; Academic Press, Inc.: Orlando, **1984**; Vol. 3, pp 341-377. (b) Sutherland, J. K. in *Comprehensive Organic Synthesis*; Trost, B. M. and Fleming, I.; Pergamon Press: Oxford, Engalnd, **1991**; Vol 3, pp 341 - 409.

3. (a) Johnson, W. S. *Acc. Chem. Res.* **1968**, *1*, 1-8. (b) Johnson, W. S. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9-17. (c) Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587 - 9595. (d) Corey, E. J.; Lin, S. *J. Am. Chem. Soc.* **1996**, *118*, 8765 – 8766. (e) Corey, E. J.; Lee, J.; *J. Am. Chem. Soc.* **1993**, *115*, 8873 – 8874. (f) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290 - 11291. (g) Corey, E. J.; Wood Jr., H. B. *J. Am. Chem. Soc.* **1996**, *118*, 11982-11983.

4. (a) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647-3655. (b) Nakamura, S.; Ishihara, K,; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8131-8140.

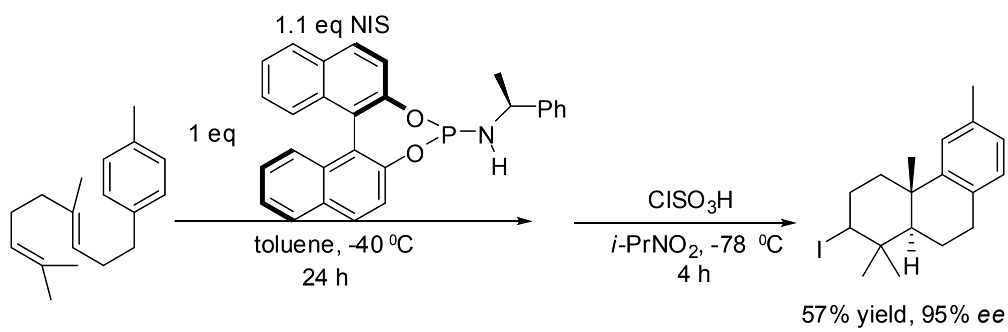
5. (a) Nishizawa, M.; Takenaka, H.; Hayashi, Y. *J. Org. Chem.* **1996**, *51*, 806-813. (b) Hoye, T. R.; Kurth, M. J. *J. Am. Chem Soc.* **1979**, *101*, 5065 – 5067.

catalysts for initiation of cation-olefin polycyclization reactions.[4] By combining a resolved BINOL derivative and a strong Lewis acid, H^+ can be delivered with a preference for one enantioface of a polyene reactant and, thereby, initiate enantioselective cation-olefin polycyclization reactions (eq. 3.1).



(3.1)

Very recently, Ishihara reported a halocyclization of polypreniods, where a combination of a chiral phosphoramidite and NIS is used to generate a chiral I^+ source. Use of these reagents with polyprenoid substrates afforded a mixture of *trans* fused halogenated bicyclic products and *trans* A ring monocyclic products in excellent *ee*. The monocyclic products can be converted to the bicyclic products by $ClSO_3H$, to yield entirely the bicyclic product (Equation 3.2).[6]



(3.2)

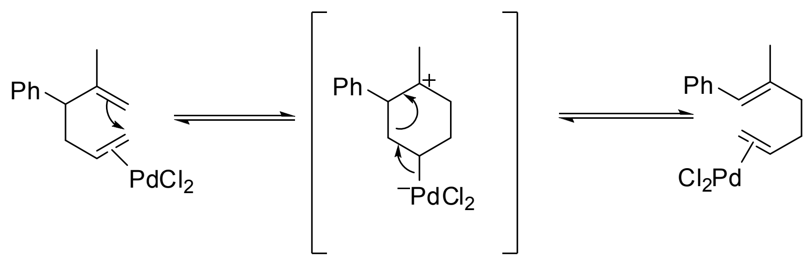
From the viewpoint of biomimetic polyene cyclizations, H^+ and I^+, like most electrophiles, prefer to activate electron rich trisubstituted alkenes and are thus well suited to initiating cation-olefin cascades to steroid-like structures. Since many natural products are geminally methylated at C-4, these efficient approaches access useful carbon skeletons.

6. Sakakura, A.; Ukai, A.; Ishihara, K. *Nature* **2007**, *445*, 900 – 903.

Conversely, ionic methods do not lend themselves to direct synthesis of 4,4-unsubstituted (e.g. cholesterol) or 4-monosubstituted carbon skeletons since this position needs to be stabilized for cation generation. This problem can be solved by oxonium ion initiation and subsequent functional group manipulation, however, the direct synthesis of materials without C-4 geminal dimethyl substitution remains a challenge.

It was in this context that previous work focused on electrophilic Pd and Pt catalysts, which have a preference for less substituted alkenes and could initiate a cascade that did not require stabilizing substitutents at C-4. The first evidence that Pd(II) could catalytically and selectivity activate terminal olefins and generate cations was reported by Overman in the $PdCl_2$-catalyzed Cope-like rearrangement (Scheme 3.1).[7] A cyclic cation was the proposed intermediate in the rearrangement; fragmentation consumed the cation and led to the diene product.

Scheme 3.13



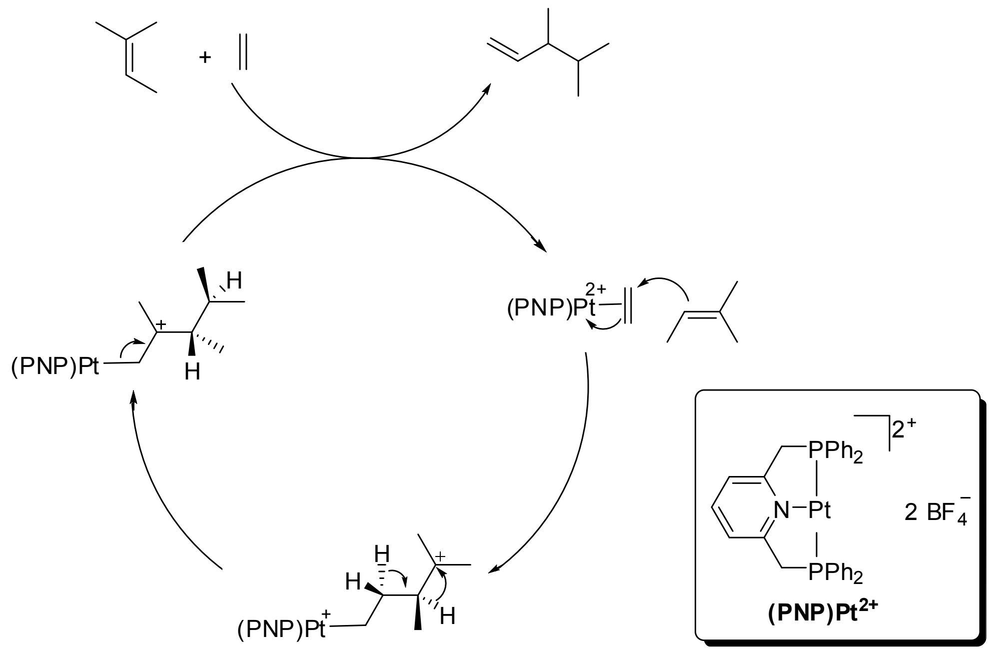
Vitaglino has reported an olefin cross dimerization that intermolecularly adds 2-methylbut-2-ene to ethylene via a 3° cation catalyzed by a pincer complex of Pt^{2+}.[8] The key feature of the proposed mechanism is the selective *anti* carbometallation of the less

7. (a) Overman, L. E.; Knoll, F. M.; *J. Am. Chem. Soc.* **1980**, *102*, 865-867. (b) Overman, L. E.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1982**, *104*, 7225-7231.

8. (a) Hahn, C.; Cucciolito, M. E.; Vitagliano, A.; *J. Am. Chem. Soc.* **2002**, *124*, 9038 – 9039. (b) Hahn, C.; Morvillo, P.; Hertweck, E.; Vitagliano, A.; *Organometallics*. **2002**, *21*, 1807 – 1818.

substituted alkene and the rearrangement of the carbocationic intermediates to expel the Pt(II) catalyst from the dimerization product.

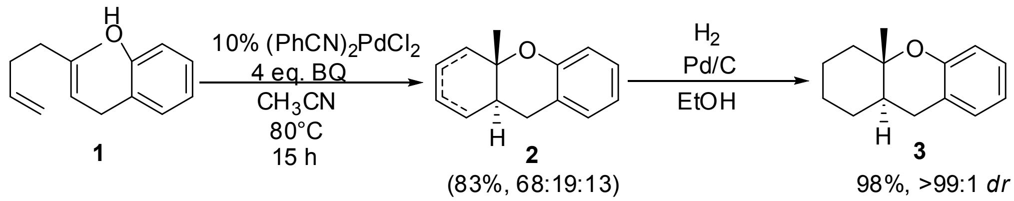
Scheme 3.14



These systems parallel cation polyene cyclizations in that carbocation intermediates are generated from C-C bond forming reactions, and that these intermediates undergo selective rearrangement and quenching. Previous work in our group therefore focused on $PdCl_2$ and pincer-Pt^{2+} as a potential new class of biomimetic cation-olefin cyclization catalysts.

Presuming that the Overman mechanism for the Cope reaction (Scheme 3.1) could be applied to polyene cyclization the $PdCl_2$ catalyzed cyclization of polyenes with intramolecular cation traps was investigated. Utilization of the optimum conditions on dienyl-phenol **1** led to its clean conversion to *trans*-fused bicycle **2** as a mixture of olefin isomers (eq. 3.3). A single product could be obtained by the hydrogenation of **2** to **3**.[9]

9. Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron*, **2004**, *60*, 7405 – 7410.



(3.3)

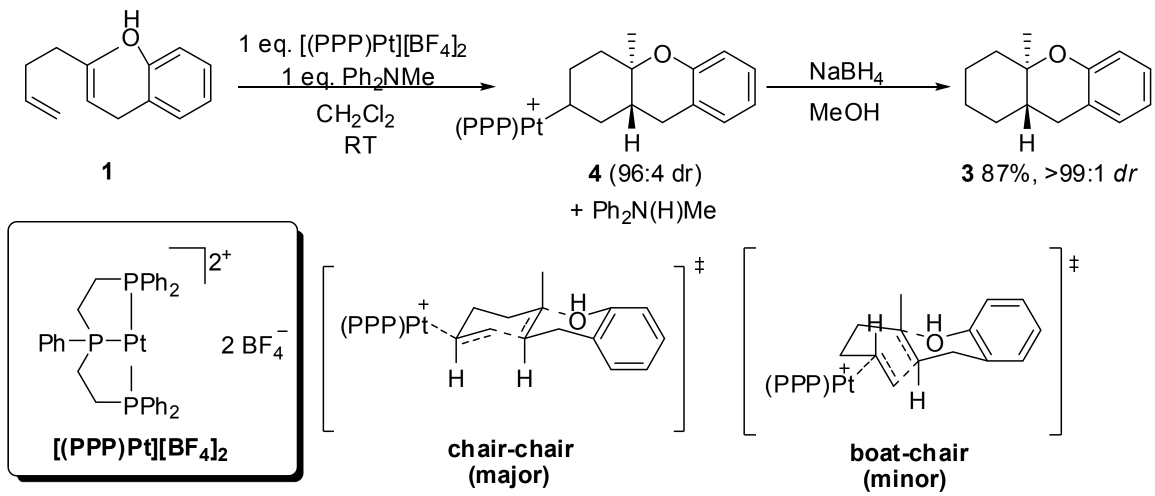
The course of the reaction was explained by cyclogeneration of a tertiary cation which is either trapped by the phenol in concert with cation generation, or very quickly thereafter since the *cis* bicycle is more stable than the observed *trans*.[10] The resulting Pd-C bond undergoes β-H elimination to generate **2** as a mixture of alkene isomers; Pd(0) to Pd(II) oxidation with benzoquinone (BQ) closes the cycle.

In addition to $PdCl_2$ catalysis, polyene cyclizations mediated by $(PPP)Pt^{2+}$ have also been examined. The triphos pincer ligand complex has a single site for alkene coordination/activation and is not prone to β-hydride elimination. The $(PPP)Pt^{2+}$ was capable of cyclizing **1** to give a cyclic Pt-alkyl, **4** (96:4 dr).[11] The addition of the weak base Ph_2NMe served to deprotonate the phenol after trapping of the putative carbocation intermediate. Reductive cleavage led to **3** as a single product, meaning the two diastereomers of **4** must be a result of epimers at the Pt-containing stereocenter. This suggested that the competing transition states during cyclization have the chair-chair and boat-chair conformations shown in Scheme 3.3.

10. Nowroozi-Isfahani, T.; Musaev, D. G.; Morokuma, K.; Gagné. M. R. *Organometallics.* Accepted.

11. Koh, J. H.; Gagné, M. R. *Angew. Chem. Int. Ed.* **2004**, *43*, 3459-3461.

Scheme 3.15

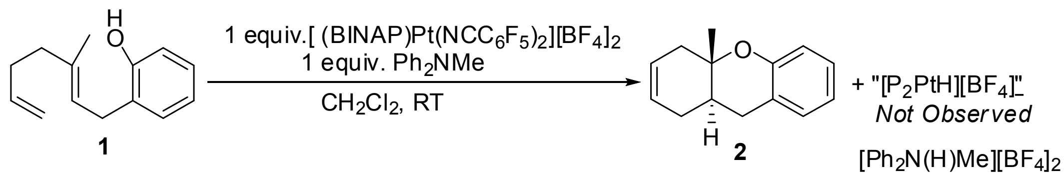


Each of these previously developed methods has its advantages and drawbacks. The $PdCl_2$ system (eq. 3.3) is an efficient catalytic system employing a common catalyst and oxidant. However, the usefulness of the oxidative cyclization products is lessened by mixtures of olefin isomers obtained. Furthermore, ligand controlled asymmetric induction is not possible because addition of donor ligands decreases the electrophilicity of the catalyst so that it is unable to activate an olefin for attack by a carbon based nucleophile. The $(PPP)Pt^{2+}$ system (Scheme 3.3) is potentially amenable to asymmetric catalysis by modification of the ligand to include chirality, however, the system is not catalytic. Experiments designed to facilitate turnover by protonolysis of Pt-C bond met with limited success because of the necessity of using a strong Brønsted acid, which catalyzed an undesired monocyclization of the substrate.[12]

We therefore simplified the Pt^{2+} complex from a pincer based system to a bisphosphine (P_2) ligated system. This opened a second coordination site on the metal so that β-hydride elimination was no longer inhibited. Use of 1 equiv. $(BINAP)Pt^{2+}$ for the oxidative polycyclization of **1** led to **2** as a *single olefin isomer* (eq 3.4). This chapter describes

12. Feducia, J. A.; Cambell, A. N.; Anthis, J. W.; Gagné, M. R. *Organometallics*, **2006**, *25*, 3114 – 3117.

reaction and catalyst development to render this oxidative polycyclization both catalytic and enantioselective.



(3.4)

3.2 Results and Discussion

A. Turnover Development. Recent advances in Wacker type oxidative cyclizations have led to Pd catalysts capable of activating and discriminating between enantiofaces of an alkene. Turnover is achieved via β-hydride elimination and traditional Pd(0) to Pd(II) oxidation protocols (O_2, BQ, $CuCl_2$, etc.).[13] However, the large majority of these systems employ neutral Pd(II) catalysts, which as mentioned above when ligated with donor ligands are not electrophilic enough to activate alkenes for nucleophilic attack by weak carbon nucleophiles. Hayashi has had success in developing BOXAX ligands for Pd-dication asymmetric Wacker cyclizations,[14] however when used as a catalyst with **1**, Pd^{2+} serves only to isomerize the terminal olefin into a more substituted position under a variety of conditions (representative experiments in Scheme 3.4). Oxidative turnover of this type with platinum[15] catalysts or with phosphine ligands is significantly less developed.

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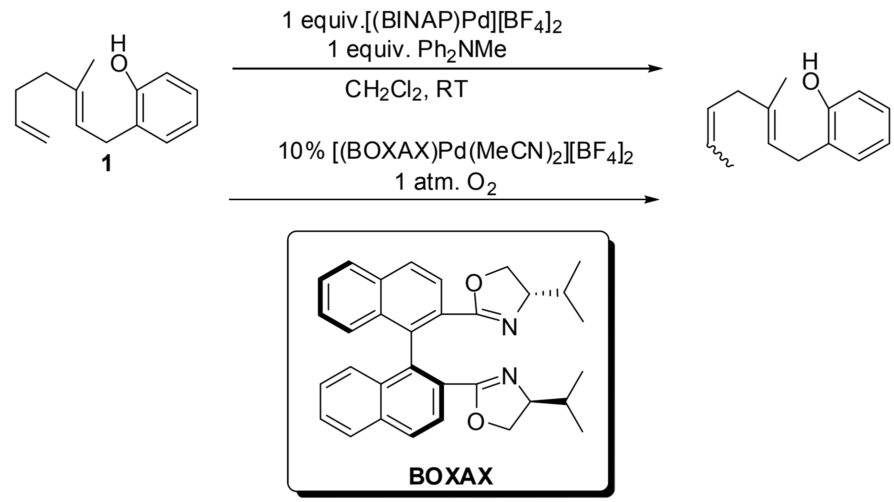
13. (a) Stahl, S. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3400 – 3420 and references therein. (b) Cornell, C. N. Sigman, M. S. *Org. Lett.* **2006**, *8*, 4117 – 4120.

14. Ubzumi, Y.; Kato, K.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 5071 – 5075.

15. Helfer, D. S.; Atwood, J. D.; *Organometallics*, **2004**, *23*, 2412 – 2420.

Scheme 3.16

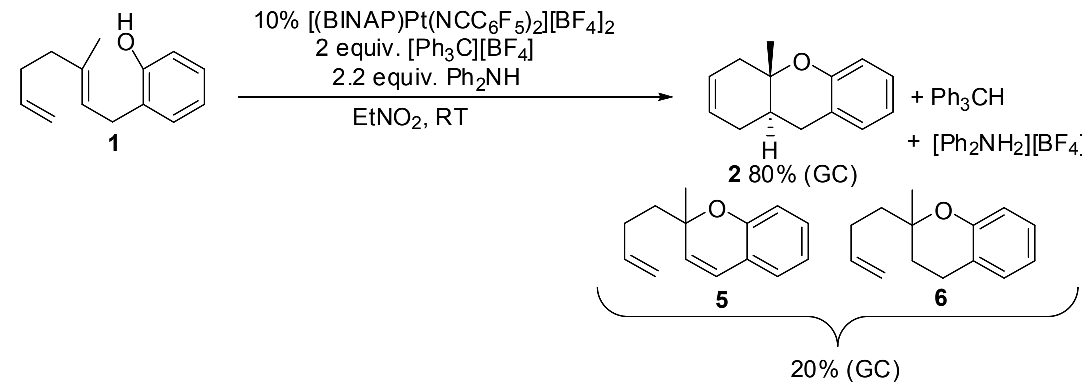


Predictably, the use of such traditional oxidants with the P_2Pt^{2+} catalysts failed to generate a catalytic system. Therefore, we reconsidered the potential reactivity of the presumed putative cationic Pt-hydride species, which we have been unable to observe. Protonation of such a species to generate H_2 and P_2Pt^{2+} is likely possible, but given the substrates sensitivity to strong Brønsted acid, it is not a viable option for the desired reactivity. However, another electrophilic reagent for the abstraction of metal hydrides, trityl cation (triphenyl carbenium),[16] proved effective in generating turnover. The use of two equivalents trityl tetrafluroborate, two equivalents Ph_2NH and 10% P_2Pt^{2+} for the polycyclization of **1** yielded **2** in greater than 90% conversion by GC, again as single olefin isomer (eq. 3.5). The amine base is necessary to trap the H^+ half of the net loss of H_2 from substrate to product; trityl cation abstraction of H^- generates triphenylmethane. The remaining 20% of **1** was converted to two monocyclization products, one oxidative (Wacker type) **5** and one mono cycloisomerization (Brønsted product) **6**. Fractions of these side products are greatly increased if a highly polar nitro solvent (nitromethane or nitroethane) is

16. (a) Cheng, T.; Bullock, R. M. *Organometallics* **2002**, *21*, 2325 – 2331. (b) Cheng, T.; Bullock, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 3150 – 3155. (c) Chen, T.; Szalda, D. J.; Zheng, J.; Bullock, R. M. *Inorg. Chem.* **2006**, *45*, 4712 – 4720.

not used (e.g. when solvent is CH_2Cl_2 **5** and **6** account for >40% of the product mixture). Control experiments showed that both of these products can result from the reaction of **1** with trityl cation alone.

Scheme 3.17



To make this protocol more convenient, we decided to replace the amine base and trityl cation with a trityl protected alcohol (a trityl ether). Trityl ethers are quickly cleaved into alcohols and trityl cation in the presence of acid. Because an equivalent of acid is generated upon each cyclization, we could generate the required amount of trityl cation *in situ* using trityl ethers. This not only removed the requirement for stoichiometric amine base which consumed the generated acid, it also decreased the concentration of highly reactive trityl cation in solution, thereby decreasing the possibility of unwanted trityl mediated side reactions.

Triphenylmethanol and a variety of trityl ethers were screened for the polycyclization of **1** with 10% P_2Pt^{2+} catalyst (Table 3.1). While triphenylmethanol was not effective in generating turnover, simple trityl ethers were, with the fraction of **2** having little dependence on the identity of the trityl ether. The exception to this was trityl *p*-OMe benzyl ether, where multiple products that were the result of the addition of *p*-OMe benzyl alcohol to **1** were observed. Because most of the trityl ethers yielded similar results, we chose the simplest one, trityl methyl ether, as the optimum trityl cation source.

Table 3.1. Effect of Various Trityl Ethers

$$\mathbf{1} \xrightarrow[\text{EtNO}_2 \quad \text{RT}]{\substack{10\%\ [(\text{BINAP})\text{Pt}(\text{NCC}_6\text{F}_5)_2][\text{BF}_4]_2 \\ 2\ \text{equiv. Ph}_3\text{CO}\mathbf{R}}} \mathbf{2 + 5 + 6}$$

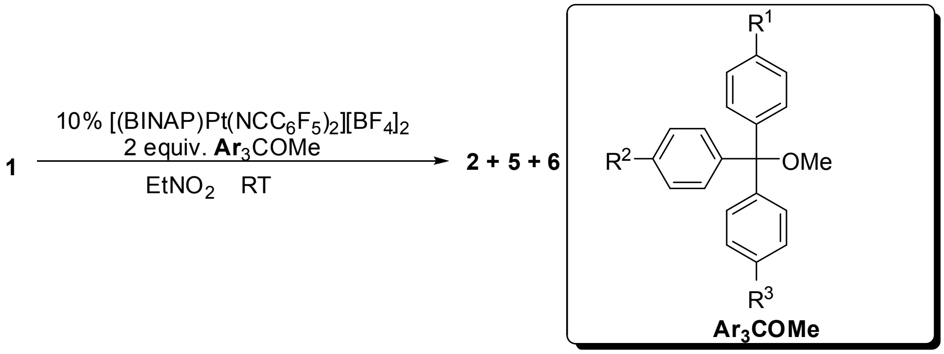
R	**% conversion**	**2:3:4(%)**
H	10%	100:0:0
Me	100%	77:12:11
CH_2CF_3	100%	73:13:14
Ph	100%	70:16:14
CH_2(*p*-OMePh)	100%	11:1:00[a]

[a] Remainder of product consisted of products of the addition of *p*-OMeBnOH to **1**.

We also screened electronic perturbations on the trityl moiety (Table 3.2). The more electron rich trityl ethers undergo cleavage faster; the introduction of *p*-methoxy groups increases the rate of hydrolysis by about one order of magnitude for each *p*-methoxy substitutent.[17] Results showed that the parent trityl methyl ether was optimum. More electron rich trityl derivatives were not strong enough hydride abstractors. The case of the electron withdrawing *p*-Cl substitutent was also not successful, probably due to a slow hydrolysis rate.

17. Greene, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*. Wiley: New York, **1999**, pp. 102 – 106.

Table 3.2. Effect of Various Trityl Methyl Ether Derivatives



R^1	R^2	R^3	% conversion	2:3:4(%)
H	H	H	100%	77:12:11
OMe	OMe	OMe	5%	100:0:0
OMe	OMe	H	5%	100:0:0
OMe	H	H	7%	100:0:0
Me	H	H	57%	81:12:7
Cl	H	H	34%	82:7:11

The conditions were further improved by employing solid state version of the trityl methyl ether oxidant, a development further necessitated by difficulties in separating the final products away from the triphenylmethane byproduct. Trityl methyl ether polystyrene resin was easily synthesized from commercially available trityl chloride resin.[18]

B. Catalyst Development. With a convenient catalytic system developed, we turned our attention to optimization of the catalyst and to the discovery of a chiral catalyst for asymmetric induction in oxidative polycyclization. A quick screen of racemic and achiral ligands revealed that (dppe)PtI_2, **7** was the best choice for an achiral precatalyst. It was also discovered that the generating the catalyst *in situ* (through halide abstraction of P_2PtX_2 with $AgBF_4$) without the addition of a labile placeholder ligand (i.e. NCC_6F_5) led to higher yields of product. This is most likely due to slow substitution of olefin for the placeholder ligand; this effect is more pronounced when a 1,2-disubstituted alkene rather than a monosubstituted

18. Fréchet, J. M.; Haque, K. E. *Tet. Lett.* **1975**, *16*, 3055 – 3056.

alkene (*vida infra*) is used at the initiating site of the polycyclization. In the same vein, nitroethane proved to be a better solvent than nitromethane, again probably due to competition of nitromethane and substrate for the catalyst's vacant coordination sites.

We next screened a large number of readily available chiral bis-phosphine ligands for generating **2** enantioselectivity (abbreviated list shown in Table 3.3). For the chiral biaryl series (BINAP, OMe-BIPHEP, see Figure 2.1) of bisphosphine ligands a marked increase in enantioselectivity was observed for the xylyl (3,5-Me_2Ph) versions over the phenyl versions (entries 3 vs. 1 and 5 vs. 4). We therefore decided employ ligands with further steric bulk in those positions by utilizing DTBM-OMe-BIPHEP and DTMB-SEGPHOS (DTMB = 3,5-ditertbutyl, 4-methoxy, entries 6 and 8); however, these catalyst with very bulky ligands did not give any conversion of **1** to **2**. Moderate enantioselectivites were also observed with BICP and BDPP chiral bisphosphine ligands. The best ligand discovered was xylyl-phanephos (Figure 3.1), where (xylyl-phanephos)Pt^{2+} catalyst yielded **2** in 75% *ee*.

Table 3.3. Representative screen of bisphosphine ligands for Pt^{2+} catalyzed polycyclization.

Entry	P_2	|% *ee*| of 2
1	(S)-BINAP	7
2	(S)-tol-BINAP	12
3	(S)-xylyl-BINAP	48
4	(*R*)-MeO-BIPHEP	12
5	(*R*)-xylyl-MeO-BIPHEP	46
6	(*R*)-DTBM-MeO-BIPHEP	NR
7	(R)-SEGPHOS	20
8	(R)-DTBM-SEGPHOS	NR
9	(R)-BICP	52
10	(R)-BDPP	41
11	(S,S)-CHIRAPHOS	20
12	(S)-xylyl-PHANEPHOS	75

Conditions: **1**, 10% P_2PtX_2 (X = Cl or I), 22% $AgBF_4$, 2.1 equiv. Ph_3COMe, $EtNO_2$.

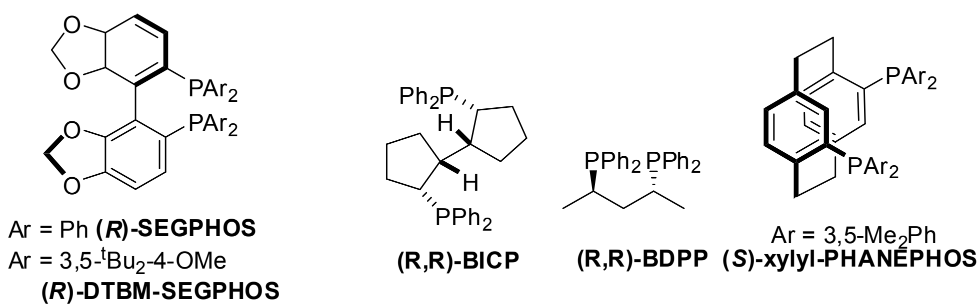


Figure 3.1. Sample structures of chiral bisphosphine ligands screened for Pt^{2+} catalyzed polycyclization.[19]

The optimum chiral precatalyst, (S)-(xylyl-phanephos)$PtCl_2$, **8** was characterized by X-ray crystallography. An ORTEP representation is shown in Figure 3.2 along with selected bond lengths and angles. As expected the Pt-P bonds are nearly equivalent; (Pt-P1 is 2.2739(12) Å and Pt-P2 is 2.2749(12) Å) as are the Pt-Cl bonds (Pt-Cl is 2.3630(13) Å and Pt-Cl2 is 2.3521(12) Å. The P1-Pt-P2 bond angle is 103.75(4)° as a consequence of the 10-membered metalacycle generated by the chelate. The complex shows little deviation from

19. For structures of binap and MeO-biphep type ligands see Figure 2.1.

planarity at Pt (Σ bond angles = 361.3°). The distortion in the aryl rings of the cyclophane backbone is evident; for example the C18-C19-C20 bond is 115.3(5)°.

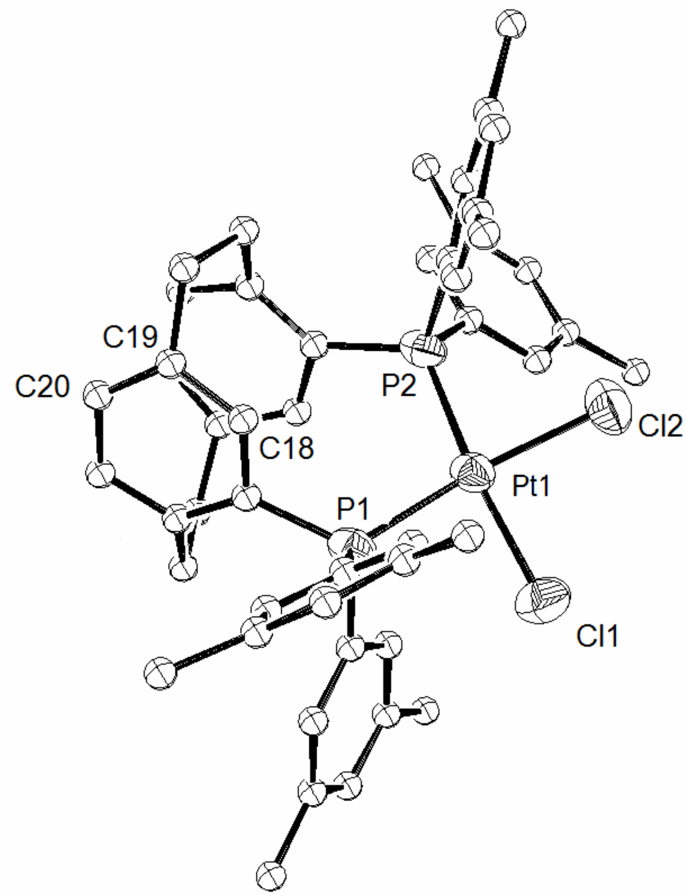
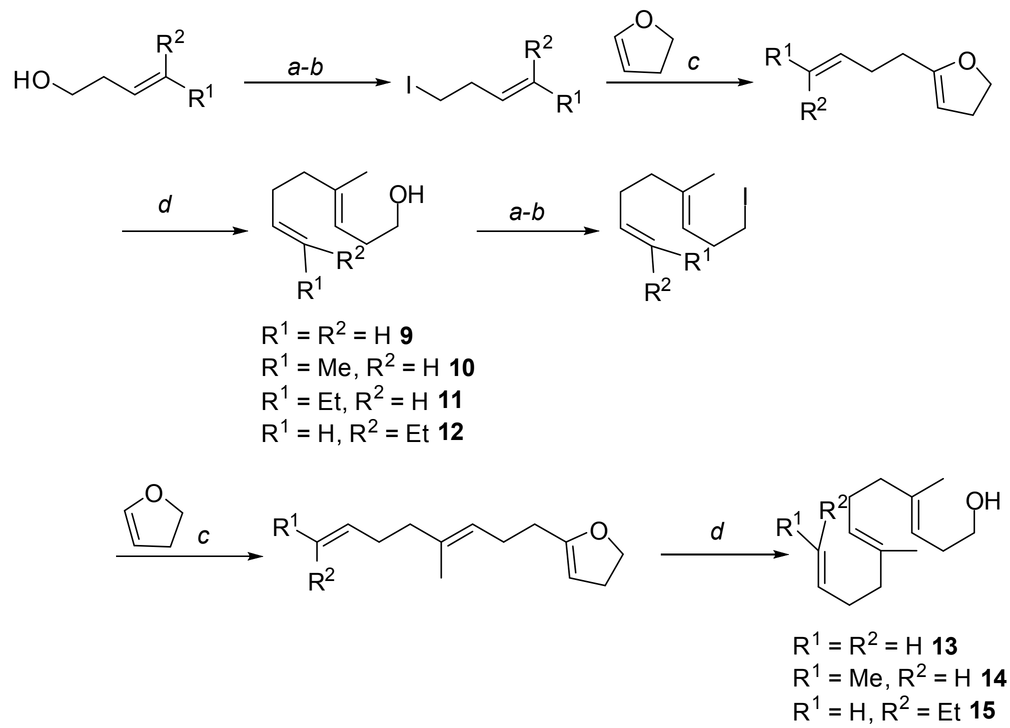


Figure 3.2. ORTEP representation of **8**.

C. Scope and Limitations. To further explore the polycyclization reactions a variety of dienol and trienol substrates were synthesized. Generally, the dienol substrates were generated from coupling of 2,3-dihydrofuran and a 1-iodo-3-butene, followed by a Ni-catalyzed addition of MeMgBr with ring opening of the dihydrofuran (Scheme 3.6). The trienol substrates were synthesized from the iodo derivative of the corresponding dienol substrates.

Scheme 3.18



Conditions: (a) $MeSO_2Cl/Et_3N$, CH_2Cl_2; (b) NaI, acetone; (c) *t*BuLi, THF; (d) $MeMgBr/(PPh_3)_2NiCl_2$, toluene.

This library of substrates was tested under the developed optimum conditions (Table 3.4). Monosubstituted alkene terminated dienol alcohol substrates **1** and **9** behaved similarly; both produced products (**2** and **16**) with *trans* ring junctions,[20] were isolated in good yield and when **8** was employed as the precatalyst enantioselectivities of 75 and 79% *ee* were achieved, respectfully. Additionally, tricyclic molecule **20**, with *trans*-anti-*trans* relative ring junction stereochemistry could be generated in very good yield and 64% *ee* from trienol substrate **13**.[21]

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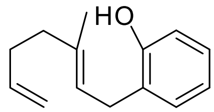
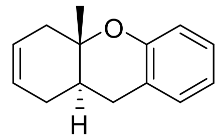
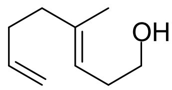
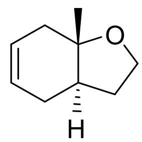
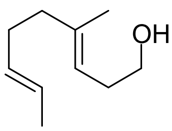
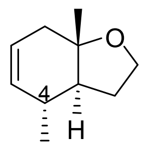
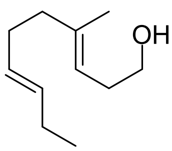
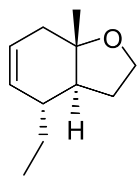
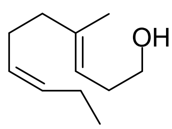
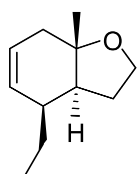
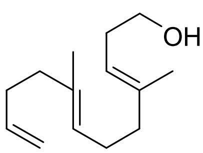
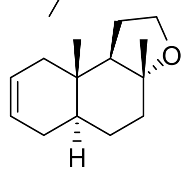
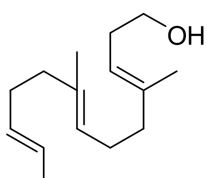
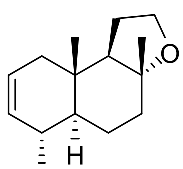
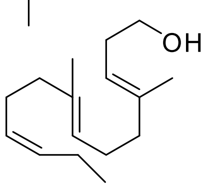
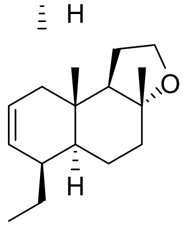
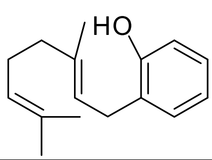
20. Trans ring junction was confirmed by comparison of the ^{1}H NMR of the hydrogenated product with the literature: see ref. 9 and Nishizawa, M.; Iwamoto, Y; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* **2000**, *2,* 1685 – 1687.

21. Trans-anti-trans relative stereochemistry determined by comparison of ^{1}H NMR of the hydrogenated product with the literature: see ref. 9 and Ohloff, G.; Giersch, W.; Pickenhagen, A. F.; Frei, B. *Hel. Chem. Acta* **1985**, *68*, 2022 – 2029.

Table 3.4. Polycyclizations catalyzed by P_2Pt^{2+}

Substrate		Precatalyst	Product		Yield[a]	%*ee*
	(**1**)	**7** **8**		(**2**)	73% 73%	 75%
	(**9**)[b]	**7** **8**		(**16**)	84% 75%	 79%
	(**10**)	**7** **8**		(**17**)	67% nd	 12%
	(**11**)	**7** **8**		(**18**)	65% nd	 10%
	(**12**)	**7** **8**		(**19**)	72% 61%	 87%
	(**13**)	**7** **8**		(**20**)	90% 76%	 64%[c]
	(**14**)	**7**		(**21**)	52%	
	(**15**)	**7**		(**22**)	45%	
	(**23**)	**7**	No Reaction			

Conditions: 10% **7** or **8**, 22% $AgBF_4$, 2.1 equiv. Ph_3COMe (resin), $EtNO_2$, RT. [a] Isolated. [b] solvent = $MeNO_2$
[c] Determined for product after hydrogenation.

The P_2Pt^{2+} catalyst proved capable of discriminating between not only mono and tri substituted alkenes, but also between 1,2-disubstituted and trisubstituted alkenes as shown by the success in cyclizing substrates **10-12** and **14-15**, generating polycyclic products that are monosubstituted at C-4. Enantioselectivity generated from use of precatalyst **8** was greatly depressed in dienol substrates **10** and **11**, containing an *E*-1,2-disubstituted alkene at the terminus. However, increases in enantioselectivity over the monosubstituted alkene terminated substrates were observed for *Z*-alkene terminated substrate **12** (87% *ee*). This dependence on olefin substitution number and stereochemistry on enantioselectivity suggests that stereochemistry is controlled by initial alkene coordination to the catalyst.

The relative stereochemistry of the products of the disubstituted products suggest that these cyclizations proceed exclusively (or nearly exclusively) through a chair transition state for A ring formation. This is surprising for *Z*-alkene terminated substrates **12** and **15**, because a 1,3-diaxial interaction is created by a chair transition state in these substrates (Figure 3.3). A boat transition state would alleviate this interaction, and is accessed in minor amounts for monosubstituted substrates in the stiochiometric cyclizations mediated by $(PPP)Pt^{2+}$ (see Scheme 3.3). Despite this, in these cyclizations the 1,3-diaxial interaction does not provide adequate driving force to disfavor the chair transition state enough to generate the seemingly accessible boat conformation.

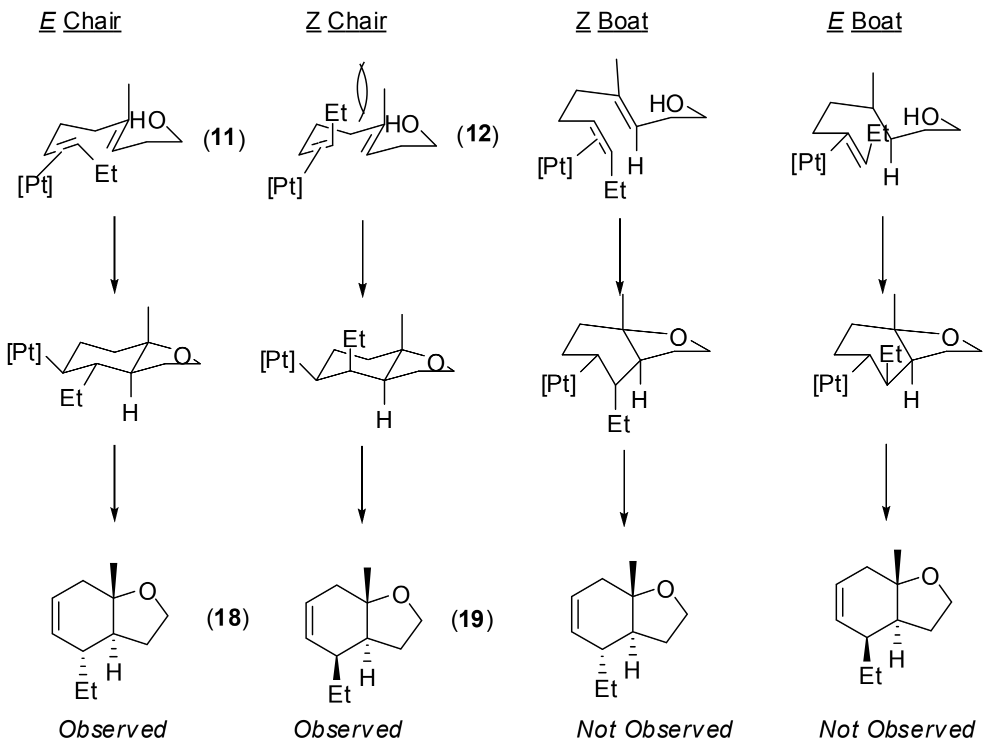


Figure 3.3. Possible and observed outcomes of chair vs. boat cyclizations for **11** and **12**.

The ability to generate C-4 epimeric structures represents an important increase in product classes that can be accessed with this methodology. While the C-4 geminally dimethylated products, a common skeleton found in natural products, could not be obtained (2-geranyl phenol (**23**) failed to cyclize), monosubstitution of the C-4 position can often induce large changes in properties versus molecules that are unsubstituted at C-4. Additionally, the C-4 epimer properties can differ. For example, Ohloff and coworkers have investigated the odors of C-4 epimers of hydrogenated **21** (**21-H$_2$**).[20] While **21-H$_2$** was described as possessing amber scent, ***epi*-21-H$_2$** (stereochemistry equal to **22** where the C-4 Et is replaced with Me) was described as having a more woody odor. Furthermore, unsubstituted structure **20-H$_2$** was described possessing a more earthy scent, reminiscent of a freshly plowed field. The substitution number and stereochemistry also dictate the strength of the odor with triaxial structure (**21-H$_2$**) stronger than both its epimer (***epi*-21-H$_2$**) and the unsubstituted **20-H$_2$** (Figure 3.3).

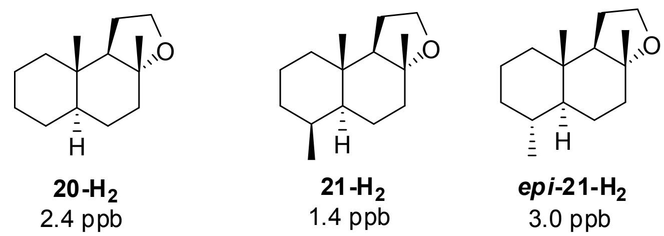
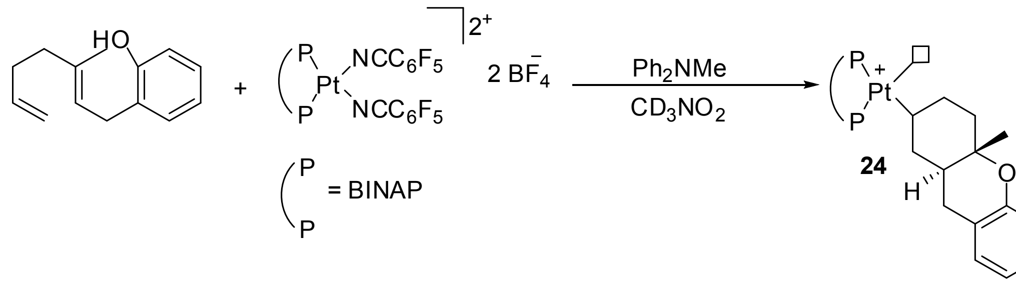


Figure 3.4. Structures available from Pt^{2+} trienol cyclizations and their odor threshold values.[20]

D. Mechanistic Considerations. Stoichiometric reaction of [(BINAP)Pt(NCC_6F_5)$_2$][BF_4]$_2$ and **1** in the presence of Ph_2NMe at 0 °C allows for clean formation of cationic Pt-alkyl intermediate, **24**, in solution as a 1:1 mixture of diastereomers (eq. 3.5). Upon warming above 0 °C, **24** undergoes β-hydride elimination to release **2** (eq. 3.4); the putative cationic Pt-H species quickly decomposes and is not observed. The ^{31}P NMR spectrum of **24** is shown in Figure 3.5. The resonance for the phosphorus *trans* to the cyclic alkyl is found at δ 21.6 appearing as a triplet because of the overlapping doublet signals of each diastereomer. The observed Pt-P coupling constant is 1555 Hz, typical of a phosphine ligand *trans* to an alkyl ligand for complexes of this type.[22] The resonance for the phosphorus *cis* to the alkyl ligand appears at δ 14.2 appearing as two doublets, one for each diastereomer. The Pt-P coupling constant is 4875 Hz, a very large value for a complex of this type and indicative of a very weakly bound species in the coordination site *trans* to this phosphine ligand.[23]

22. (a) Piddcock, A.; Richards, R. E.; Venanzi, L. M. *J. Chem. Soc. A* **1966**, 1707 – 1710. (b) Appleton, T. G.; Bennett, M. A. *Inorg. Chem.* **1978**, *17*, 738 – 747.

23. Because of the *trans* effect in square planar complexes strong ligands *trans* to a phosphine lignad weaken the Pt-P bond and decrease the value of the coupling constant; therefore larger coupling constants are indicative



(3.5)

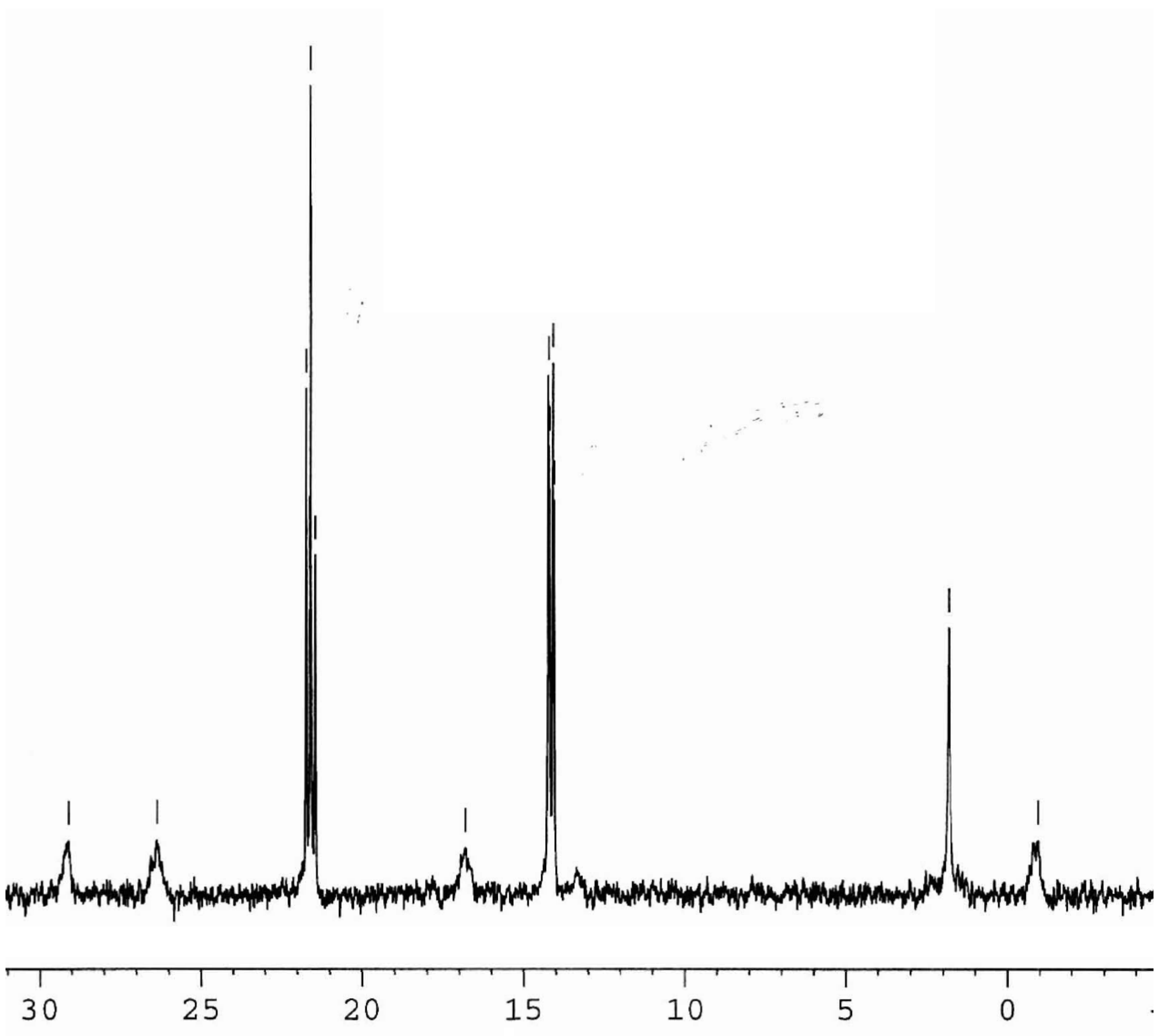


Figure 3.5. ^{31}P NMR spectrum of **24** in CD_3NO_2 at 273K.

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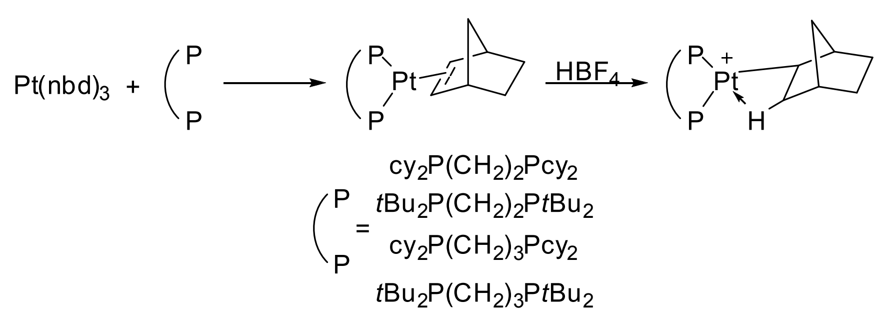
of weak ligands in the *trans* position. For comparison the weak ligand species $[(BINAP)Pt(NCC_6F_5)_2][BF_4]_2$ and $[(BINAP)Pt(MeNO_2)_2][BF_4]_2$ exhibit P-Pt coupling constants of 3720 Hz and 4145 Hz respectively.

Despite the seemingly very weak ligand occupying the fourth coordination site of **24**, addition of excess amounts of good ligands such as acetonitrile and triflate anion did not cause any change in **24**.[24] We therefore hypothesized that the weak ligand was a β-H agostic interaction from the cyclic alkyl ligand and this interaction with Pt, although weak was geometrically accessible. Such agostic interactions have been observed before for bis(phosphine)Pt-alkyl cations. Spencer has prepared a series of coordinatively unsaturated bis(phosphine)Pt-norbornyl cations (Scheme 3.7) and has confirmed the presence of a β-agostic interaction by x-ray crystallography.[25] The observed Pt-P coupling constants for the phosphine *cis* to the norbornyl ligand (*trans* to the agostic) ranged from 3866 to 5067 Hz for various ethylene and propylene linked alkyl phosphine ligands. Reproducing Spencer's synthesis with BINAP as the bisphosphine ligand has led to a complex with ^{31}P NMR spectral data in excellent agreement with that of **24**,[26] lending strong evidence in support of an agostic interaction in **24**.

Scheme 3.19.

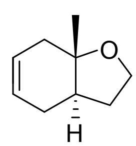


24. CO and CN$^-$ did react with **24**, however, the products have not been identified or well characterized.

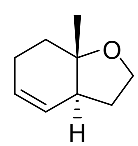
25. (a) Carr, N.; Dunne, B. J.; Orpen, A. G.; Spencer, J. L.; *J. Chem. Soc. Chem. Commun.* **1988**, 926 – 928. (b) Carr, N.; Mole, L.; Orpen, A. G.; Specer, J. L. *J. Chem. Soc. Dalton Trans.* **1992**, 2653 – 2662.

26. Campbell, A. N.; Gagné, M. R.; *Unpublished Results.*

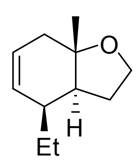
One of the major improvements of this chemistry over the $PdCl_2$ methodology is the olefin regioselectivity. An agostic interaction such as that proposed for Pt-alkyl intermediate **24**, provides an explanation for selective β-hydride elimination leading to a single olefin isomer of product. As shown in Figure 3.6, the thermodynamic stability of the products can explain the preference in the products for the monosubstituted alkene terminated substrates (products **2**, **16**, and **20**), however, for *cis* disubstituted alkene substrates (products **19** and **22**) the most stable isomer is not the one observed. The *trans*-disubstituted alkene terminated substrates can only give the observed regioisomer because there is not a Pt-coplanar hydride at C-4 in the proposed Pt-equatorial chair intermediate (see Figure 3.3). A kinetic preference for the observed regioisomer provided by preorganization through the agostic interaction with Pt could explain the observed regioselectivity.



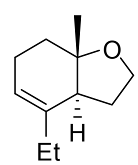
16
ΔH^0_{rel} = 0 kcal/mol



Not Observed
ΔH^0_{rel} = +3.56 kcal/mol



19
ΔH^0_{rel} = +2.31 kcal/mol



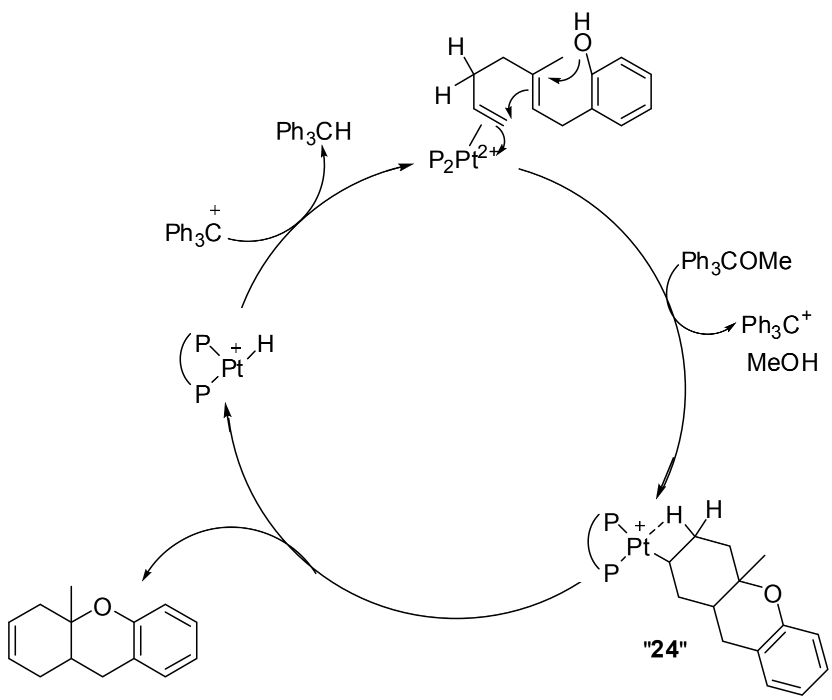
Not Observed
ΔH^0_{rel} = 0 kcal/mol

Figure 3.6. Calculated[27] relative heats of formation of possible regioisomers of products 1**6** (top) and **19** (bottom).

27. MacSpartin '04, semi-empirical, AM1.

Trityl cation, in addition to abstracting hydride from metal-hydrides[15] is also known to abstract β-hydrides[28] or α-hydrides[29] from metal-alkyl species, to form olefin complexes and metal-carbenes respectfully. Despite the fact that we have been operating under the assumption that β-hydride elimination followed by abstraction of the Pt-H was the turnover mechanism for this reaction, any of these mechanisms could be operative to generate the observed products.

Scheme 3.20



The proposed catalytic cycle for the elimination/abstraction mechanism for the polycyclization of **1** is shown in Scheme 3.8. Electrophilic activation of the terminal olefin by P_2Pt^{2+} initiates cyclization and generates the cyclic cationic Pt-alkyl species (**24** if P_2 = BINAP). In the process the H^+ generated cleaves Ph_3COMe in to trityl cation and methanol.

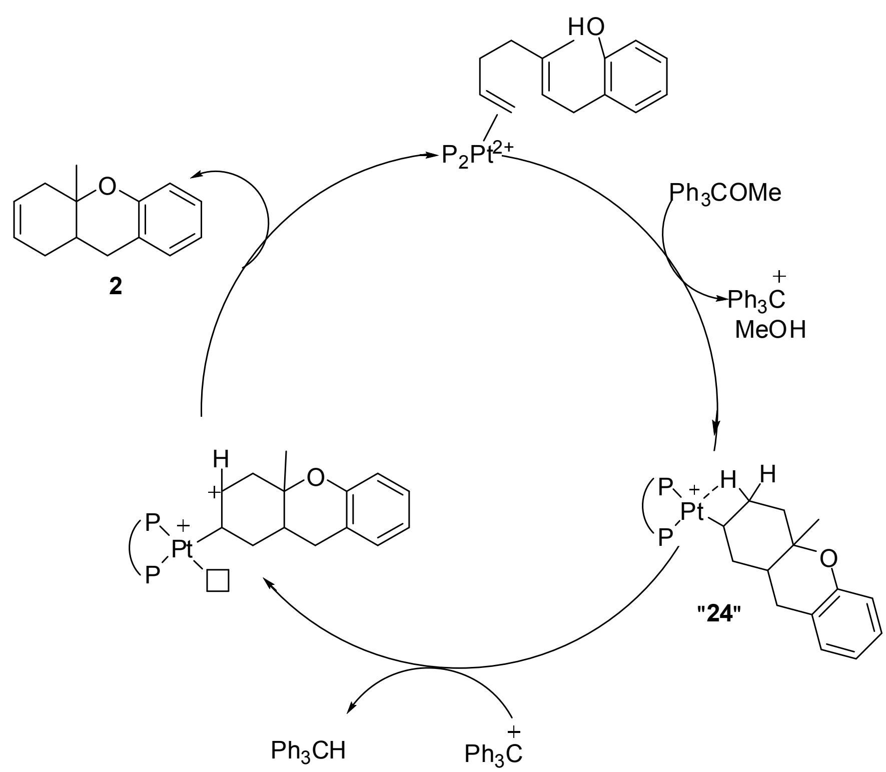
28. For an example see: Laycock, D. E.; Baird, M. C. *Tet. Lett.* **1978**, 3307 – 3308.

29. For an example see: Cooper, N. J.; Hayes, J. C. *J. Am. Chem. Soc.* **1982**, *104*, 5570 – 5572.

Next, "**24**" undergoes β-hydride elimination to generate at cationic P_2Pt-hydride species. The active catalyst is then regenerated by abstraction of the putative hydride from Pt.

A second possibility is that the observed β-agostic interaction weakens the C-H bond in that position and the opportunistic trityl cation abstracts this hydride directly from the cationic Pt-alkyl (Scheme 3.9). This generates a carbocation β to the Pt-C bond which causes the η^1-alkyl to slip to the Pt^{2+} η^2-olefin species, releasing **2** upon substitution by another molecule of **1.**

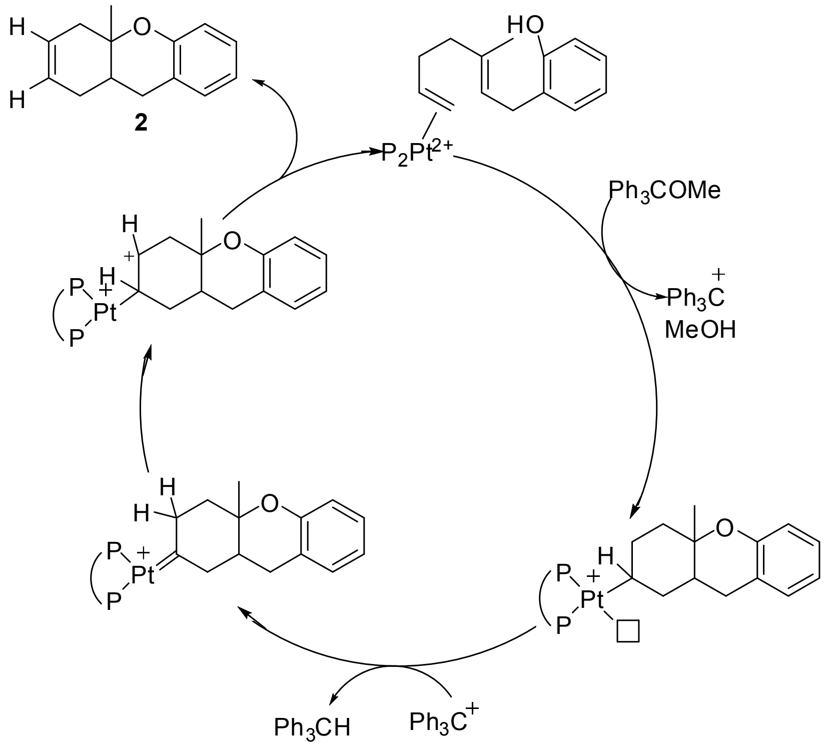
Scheme 3.21.



The third possible mechanism results from trityl cation abstraction of the hydride α to the Pt-C bond (Scheme 3.10). This results in a cationic Pt-carbene species. While an unusual structure, cationic Pt(II) and Au(I) carbenes have been postulated to be key intermediates in

1,6-enyne cycloisomerizations.[30] The product is released through a 1,2-hydride shift to generate the same β-cationic Pt-alkyl as proposed in the β-abstraction mechanism (Scheme 3.9), followed by η^1-η^2 slippage and alkene displacement.

Scheme 3.22



Strong circumstantial evidence suggests that elimination/abstraction is operative. For example, the (PPP)Pt^{2+} catalysts where β-hydride elimination is inhibited are not subject to turnover by trityl cation. Additionally, turnover does not occur at 0 °C, where **24** is stable to β-hydride elimination. Also, the sterically demanding DTMB-SEGPHOS ligand, whose Pt^{2+} catalysts produced no conversion from **1** to **2** under catalytic conditions (see table 3.3), is capable of forming the cyclic Pt-alkyl cation analogous to **24**. In this case the complex is stable to β-hydride elimination at room temperature, thus showing that the large ligand

30. López, S.; Herrero-Gómez, E.; Pérez-Galán, P; Nieto-Oberhuber, C; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1 – 4. (b) Méndez, M.; Mamane, V.; Fürstner, A. *Chemtracts-Org. Chem*. **2003**, *16*, 397 – 425.

inhibits β-hydride elimination, not coordination and cyclization of **1**. Lack of catalytic activity in these cases, provides further evidence that β-hydride elimination is necessary for catalysis.

3.3 Conclusion

A regio-, diastereo- and enantio-selective biomimetic oxidative polycyclization catalyzed by bis(phosphine)Pt-dications has been developed. Utilization of the commercially available ligand xylyl-PHANEPHOS provided optimum enantioselectivities, up to 87%. The use of trityl cation as the stoichiometric oxidant where traditional oxidants failed was the key development in generating a catalytic system. The scope of this reaction includes various dienol and trienol substrates for generation of a variety of polycyclic structures. The reaction also proved to be stereospecific with various epimeric products possible, dependant on the *E* or *Z* geometry of the substrates. The proposed mechanism for this reaction involves electrophilic activation of the least substituted olefin of a polyenol, and cationic cyclization to generate a coordinatively unsaturated Pt-alkyl cation intermediate exhibiting a β-agostic interaction to Pt. Selective β-hydride elimination releases the product as a single regioisomer. The cycle is proposed to close via abstraction of the putative Pt-hydride by trityl cation. This reaction represents an important improvement over previously developed late metal mediated biomimetic polycyclizations as it combines the two important features of efficient catalytic turnover and ligand induced stereocontrol.

3.4 Experimental

General Procedures:

Synthetic procedures were performed under nitrogen using standard Schlenk techniques or in a nitrogen filled glove box. CH_2Cl_2, THF, and toluene were sparged with argon and passed through a column of activated alumina. $MeNO_2$ and $EtNO_2$ were distilled from CaH_2. (*S*)-xylyl-PHANEPHOS was purchased from Strem and used as received. Polycyclization substrates **1**, **9**, **13**,[9] **23**,[31] Ph_3COMe (and other TrOMe derivatives),[32] Ph_3COMe[33] resin and (cod)$PtCl_2$[34] were prepared according to literature procedures. (dppe)PtI_2 was prepared from dppe and (cod)PtI_2.[33] NMR spectra were recorded on a Bruker 400 MHz Avance; chemical shifts are reported in ppm and referenced to residual solvent peaks (^1H and ^{13}C) or to an external standard (85% H_3PO_4, ^{31}P). GC was performed on an HP-6890. High-resolution mass spectrometry was performed by the Mass Spectrometry Laboratory at the University of North Carolina at Chapel Hill.

Synthesis of Polycyclization Substrates:

(3*E*,7*E*)-4-methylnona-3,7-dien-1-ol (10): A solution of MeMgBr in ether (18.2 mL, 50.9 mmol) was added to a stirred suspension of $(PPh_3)_2NiCl_2$ (556 mg, 0.85 mmol) in 60 mL dry toluene under nitrogen. The resulting red solution was stirred at room temperature for 15 min, and a solution of (*E*)-5-(hex-4-enyl)-2,3-dihydrofuran (2.36 g, 17.0 mmol) in toluene (20 mL) was added. The mixture was then heated to reflux for 1 h. The reaction was then cooled to 0 °C and transferred via cannula to a 50% aqueous solution of $NaCO_3$. The

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31. Yamad, S.; Ono, F.; Katagiri, T.; Tanaka, J. *Bull. Chem. Soc. Jap.* **1977**, *50*, 750-755.

32. Huszthy, P.; Lempert, K.; Simig, G.; Vékey, K. *J. Chem. Soc. Perkin Trans. I*, **1982**, 3021 – 3025.

33. Fyles, T. M.; Leznoff, C. C. *Can. J. Chem.* **1976**, *54*, 935 – 942.

34. Drew, D.; Doyle, J. R. *Inorg. Syn.* **1990**, *28*, 346-349.

mixture was stirred vigorously until it decolorized (30 min) and was then extracted with diethyl ether. The combined extracts were dried with $MgSO_4$ and the solvent removed *in vacuo*. The crude material was purified by column chromatography on silica gel eluted with 9:1 hexanes: EtOAc to yield 1.97g **10** as a colorless oil (75%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.36 (m, 2H), 5.10 (m, 1H), 3.59 (q, J = 5.6 Hz, 2H), 2.26 (q, J = 6.8 Hz, 2H), 2.07 (m, 4H), 1.62 (d, J = 5.2 Hz, 3H), 1.61 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ

(3*E*,7*E*)-4-methyldeca-3,7-dien-1-ol (11): A procedure similar to that used for synthesis of **10** was followed. The crude material was purified by column chromatography on silica gel eluted with 9:1 hexanes: EtOAc to yield **11** as a colorless oil (78%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.43 (m, 1H), 5.33 (m, 1H), 5.09 (t, J = 7.2 Hz, 1H), 3.58 (q, J = 6.4 Hz, 2H), 2.26 (q, J = 6.8 Hz, 2H), 2.08 (m, 4H), 1.95 (quintet, J = 7.2 Hz, 2H), 1.61 (s, 3H), 1.42 (t, J = 6.0 Hz, 1H), 0.93 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.7, 132.3, 128.6, 120.0, 62.3, 39.8, 31.4, 31.0, 25.5, 16.2, 13.9. HRMS expected for $C_{11}H_{20}O$+H: 169.159. Found: 169.157.

(3*E*,7*Z*)-4-methyldeca-3,7-dien-1-ol (12): A procedure similar to that used for synthesis of **10** was followed. The crude material was purified by column chromatography on silica gel eluted with 9:1 hexanes: EtOAc to yield **12** as a colorless oil (56%). ^{1}H NMR ($CDCl_3$, 400 MHz): **^{1}H** NMR (400 MHz, $CDCl_3$) δ 5.35 (m, 1H), 5.27 (m, 1H), 5.11 (t, J = 7.2 Hz, 1H), 3.59 (q, J = 6.0 Hz, 2H), 2.27 (q, J = 6.8 Hz, 2H), 2.13 (q, J = 7.6 Hz, 2H), 2.02 (m, 4H), 1.62 (s, 3H), 1.44 (t, J = 5.6 Hz, 1H), 0.93 (t, J = 7.6 Hz, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 138.6, 131.9, 128.5, 120.1, 62.3, 39.7, 31.4, 25.5, 20.5, 16.1, 14.4. HRMS expected for $C_{11}H_{20}O$+H: 169.159. Found: 169.159.

(3*E*,7*E*,11*E*)-4,8-dimethyltrideca-3,7,11-trien-1-ol (14): A procedure similar to that used for synthesis of **10** was followed.. The crude material was purified by column chromatography on silica gel eluted with 9:1 hexanes: EtOAc to yield **14** as a colorless oil (62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.39 (m, 2H), 5.09 (m, 2H), 3.59 (q, *J* = 6.4 Hz, 2H), 2.27 (q, *J* = 6.8 Hz, 2H), 2.02 (m, 8H), 1.62 (d, *J* = 5.2 Hz, 3H), 1.61 (s, 3H), 1.58 (s, 3H), 1.37 (t, *J* = 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.9, 135.1, 131.1, 124.7, 124.0, 119.8, 62.4, 39.8, 39.7, 31.5, 31.2, 26.4, 17.9, 16.2, 16.0. HRMS expected for $C_{15}H_{26}O$+H: 223.206. Found: 223.205.

(3*E*,7*E*,11*Z*)-4,8-dimethyltetradeca-3,7,11-trien-1-ol (15): A procedure similar to that used for synthesis of **10** was followed.. The crude material was purified by column chromatography on silica gel eluted with 9:1 hexanes: EtOAc to yield **14** as a colorless oil (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.31 (m, 2H), 5.09 (m, 2H), 3.59 (q, *J* = 6.4 Hz, 2H), 2.27 (q, *J* = 6.8 Hz, 2H), 2.09 (m, 4H), 2.00 (m, 6H), 1.62(s, 3H), 1.58 (s, 3H), 1.38 (t, *J* = 6.0 Hz, 1H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 135.0, 131.6, 128.7, 124.1, 119.8, 62.4, 39.8, 39.6, 31.4, 26.4, 25.6, 20.5, 16.2, 16.0, 14.4. HRMS expected for $C_{16}H_{28}O$+H: 237.222. Found: 237.222.

Synthesis of Precatalyst:

(*S*)-(xylyl-PHANEPHOS)PtCl$_2$ (8): A solution of (S)-xyly-PHANEPHOS (500 mg, 0.73 mmol) in 25 mL CH_2Cl_2 was slowly added to a solution of (cod)PtCl$_2$ (272 mg, 0.73 mmol) in 25 mL CH_2Cl_2. After 30 min of stirring the solvent was removed in *vacuo* and the yellow solid precipitated from CH_2Cl_2/hexanes and isolated by filtration on a frit. The white power was then washed with generous amounts of hexanes and dried *in vacuo* to yield 634 mg (91%) of **8**. ^{31}P NMR (162 MHz, CD_2Cl_2) δ24.3 (s, $J_{P\text{-}Pt}$ = 3904 Hz). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.53 (d, J = 10.8 Hz, 3H), 7.48 (d, J = 17.6 Hz, 3H), 7.24 (s, 2H), 7.05 (s, 2H), 6.45 (d, J = 8.0 Hz, 2H), 6.33 (m, 2H), 2.60 (m, 2H), 2.50 (m, 2H), 2.37 (s, 12H), 2.28 (s, 3H). Crystals suitable for X-ray diffraction obtained by vapor diffusion of *n*-pentane to a nearly saturated solution of **8** in CH_2Cl_2.

Oxidative Polycyclizations:

General Procedure: To a 13.3 mM solution of P_2PtX_2 ((S)-xylyl-PHANEPHOS)$PtCl_2$ (**8**) or (dppe)PtI_2 (**7**) (typically 0.02 mmol) in $EtNO_2$ (or $MeNO_2$ for susbtrates **1**, **9**, and **13**) was added 2.2 equiv. $AgBF_4$. After stirring 1 h in the dark, 21.0 equiv. Ph_3COMe on polystyrene resin, 1 equiv. Ph_2NH, and 10 equiv. substrate were added and the mixture was stirred at room temperature in the dark until the reaction was complete by GC (typically 6-8 h). The reaction mixture was then quenched by passage through plug of silica gel eluted with ether. Solvent was then removed *in vacuo*. Yields obtained with precatalyst **7** appear in brackets. Enantioselectivity data for products obtained using precatalyst **8**.

***Trans*-4α-methyl-4,4α,9,9α-tetrahydro-1H-xanthene (2).** Prepared from **1**. Crude material purified by flash chromatography on silica gel eluted with 3:97 ethyl acetate:hexanes. 29.2 mg (73% yield) [29.5 mg (73% yield)]. Enantiomeric excess determined by GC: t_R 40.4 min (major); t_R 40.2 min (minor) [Agilent Cyclosil (30M x 0.25mm), H_2, 20 psi, 80 °C hold 5 min, ramp 2°C/min to 170°C] as 75%. $[\alpha]^{25}$ = +9.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (t, J =7.6 Hz, 1H), 7.01 (d, J = 7.6 Hz, 1H), 6.77 (q, J = 7.6 Hz), 5.63 (m, 2H), 2.71 (dd, J = 16.4 Hz, 5.2 Hz, 1H), 2.51 (m, 1H), 2.35 (m, 3H), 2.15 (m, 1H), 1.78 (m, 1H), 1.20 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 129.3, 127.3, 125.4, 125.2, 121.5, 119.7, 117.0, 75.7, 39.9, 35.1, 31.9, 28.9, 17.4. HRMS expected for $C_{14}H_{16}O$+H: 201.128. Found: 201.127.

***Trans*-7α-methyl-2,3,3α,4,7,7α-hexahydrobenzofuran (16):** Crude material purified by flash chromatography on silica gel with eluted with 3:97 diethyl ether:pentane. 21.0 mg (76% yield) [(23.0 mg (84% yield)]. Enantiomeric excess determined by GC: t_R 10.0 min (major); t_R 9.7 min (minor) [Agilent Cyclosil (30M x 0.25mm), H_2, 20 psi, 80° C hold 8 min, ramp 20°C/min to 170°C] as 79%. $[\alpha]^{25}$ = +17.8 (*c* 0.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.62 (m, 2H), 3.90 (dd, *J* = 8.4 Hz, 3.2 Hz, 1H), 3.84 (m, 1H), 2.32 (m, 1H), 2.23 (m, 2H), 1.96 (m, 1H), 1.64 – 1.86 (m, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.5 (2C), 79.5, 65.0, 43.3, 40.1, 29.0, 28.4, 17.1. HRMS expected for $C_9H_{14}O$+H: 139.112. Found: 139.110.

(*Trans-anti*)-4,7α-dimethyl-2,3,3α,4,7,7α-hexahydrobenzofuran (17): Crude material purified by flash chromatography on silica gel eluted with 3:97 diethyl ether:pentane. [20.3 mg (67% yield)] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.56 (m, 1H), 5.43 (m, 1H), 3.92 (dt, *J* = 9.6 Hz, 3.2 Hz, 1H), 3.83 (q, *J* = 8.4 Hz), 2.18 (m, 2H), 2.00 (m, 2H), 1.63 (m, 1H), 1.39 (m, 1H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.2, 125.3, 79.8, 65.2, 39.9, 34.8, 27.1, 19.7, 17.9. HRMS expected for $C_{10}H_{16}O$+H 153.128. Found: 153.126.

(*Trans-anti*)-4-ethyl-7α-methyl-2,3,3α,4,7,7α-hexahydrobenzofuran (18): Crude material purified by flash chromatography on silica gel eluted with 3:97 diethyl ether:pentane. [19.8 mg (65% yield)]. ^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.60 (m, 1H), 5.54 (m, 1H), 3.91 (dt, *J* = 8.3 Hz, 2.8 Hz, 1H), 3.84 (q, *J* = 8.4 Hz, 1H), 2.19 (m, 2H), 2.00 (m, 1H), 1.86 (bm, 1H), 1.57 – 1.67 (m, 2H), 1.45 – 1.55 (m, 2H), 1.33 (m, 1H), 0.95 (s, 3H), 0.93 (t, *J* = 8.0 Hz). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 130.9, 125.9, 80.0, 65.2, 48.6, 41.3, 40.0, 29.7, 27.3, 26.6, 17.8, 11.0. HRMS expected for $C_{11}H_{18}O$+H: 167.144. Found: 167.142.

(*Trans-syn*)-4-ethyl-7α-methyl-2,3,3α,4,7,7α-hexahydrobenzofuran (19): Crude material purified by flash chromatography on silica gel eluted with 3:97 diethyl ether:pentane. 18.5 mg (61% yield) [21.9 mg (72% yield)]. Enantiomeric excess determined by GC: t_R 12.0 min (major); t_R 11.9 min (minor) [Agilent Cyclosil (30M x 0.25mm), H_2, 20 psi, 80 °C hold 8 min, ramp 20°C/min to 170°C] as 87%. $[\alpha]^{25}$ = +61.7 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.78 (m, 1H), 5.62 (m, 1H), 3.92 (m, 1H), 3.83 (q, *J* = 8.0 Hz, 1H), 2.30 (br m, 1H), 2.20 (m, 1H), 1.98 (m, 2H), 1.56 (m, 1H), 1.29 (m, 2H), 0.99 (s, 3H), 0.95 (t, *J* = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.1, 124.9, 78.6, 64.6, 46.2, 40.3, 40.1, 25.2, 21.7, 20.5, 13.2. HRMS expected for $C_{11}H_{18}O$+H 167.144. Found: 167.143.

20: Crude material purified by flash chromatography on silica gel eluted with 3:97 EtOAc:hexanes. 31.3 mg (76% yield) [(37.1 mg (90% yield)]. Enantiomeric excess determined for **20-H₂** (*vida infra)* as 64%. $[\alpha]^{25}$ = +18.2 (*c* 0.5, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.63 (m, 1H), 5.53 (m, 1H), 3.92 (m, 1H), 3.83 (q, *J* = 8.4 Hz, 1H), 1.87 (m, 1H), 1.82 (m, 2H), 1.78 (m, 1H), 1.56 (m, 2H), 1.40 (m, 4H), 1.26 (m, 2H), 1.08 (s, 3H), 0.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 126.7, 125.2, 80.0, 67.8, 57.7, 42.9, 40.8, 38.6, 34.0, 28.7, 27.5, 22.8, 20.5, 12.0. HRMS expected for $C_{14}H_{22}O$+H: 207.175. Found: 207.173.

20-H_2: To a solution of 5 mg **20** (0.024 mmol) in 1.0 mL Et_2O was added 5 mg Pd/C (0.002 mmol Pd). The atmosphere was saturated with H_2 (ballon) and the mixture was stirred under H_2 for 3h. The solution was then filtered through a PTFE filter and concentrated to yield 3 mg **20-H_2** (60% yield). ^1H NMR matched the literature data.[20]

Enantiomeric excess determined by GC: t_R 48.4 min (major); t_R 49.3 min (minor) [Agilent Cyclosil (30M x 0.25mm), H_2, 7.5 psi, 135 °C isothermal] as 64%.

21: Crude material purified by flash chromatography on silica gel eluted with 3:97 EtOAc:hexanes. [(22.9 mg (52% yield)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.61 (m, 1H), 5.48 (m, 1H), 3.93 (m, 1H), 3.83 (q, J = 8.4 Hz, 1H), 2.17 (m, 2H), 1.94 (m, 2H), 1.66 (m, 1H), 1.50 (m, 4H), 1.32 (m, 2H), 1.09 (s, 3H), 0.83 (d, J = 6.4 Hz, 3H), 0.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.1, 125.7, 79.6, 65.0, 59.0, 57.4, 46.3, 41.4, 40.4, 38.7, 25.2, 22.2, 20.7, 15.8, 13.4.

22. Crude material purified by flash chromatography on silica gel eluted with 3:97 EtOAc:hexanes [(21.0 mg (45% yield)]. ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.87 (m, 1H), 5.55 (m, 1H), 3.91 (m, 1H), 3.83 (q, J = 8.0 Hz, 1H), 1.95 (m, 2H), 1.83 (m, 2H), 1.75 (m, 3H), 1.58 (m, 4H), 1.43 (m, 2H), 1.22 (m, 2H), 1.09 (s, 3H), 0.93 (t, J = 7.6 Hz, 3H), 0.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.2, 123.8, 79.9, 64.8, 58.8, 46.3, 41.4, 40.9, 39.0, 34.5, 25.1, 22.6, 22.2, 20.3, 15.6, 13.6.

Appendix A

Crystal Structure of (*S*)-(xylyl-PHANEPHOS)$PtCl_2$

(**8**, Chapter 3)

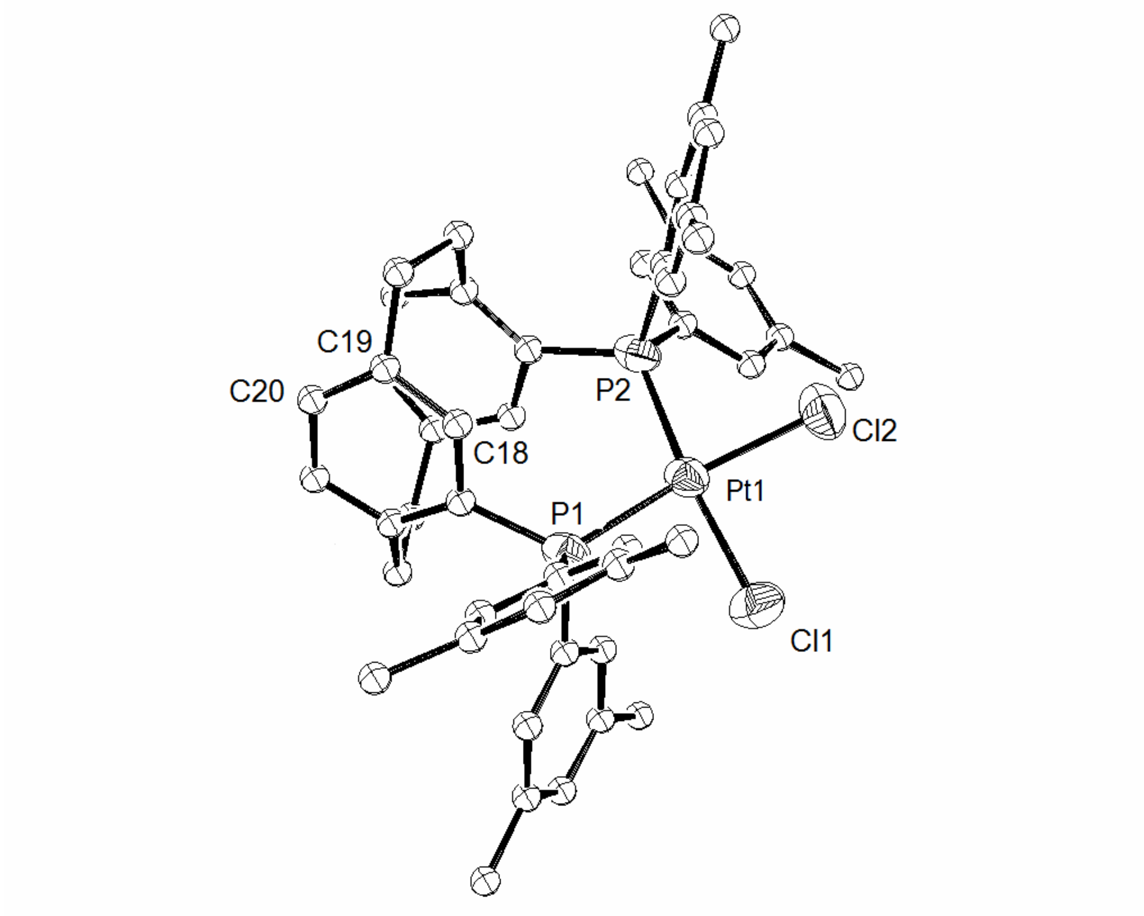

Figure A.1 ORTEP representation of (*S*)-(xylyl-PHANEPHOS)$PtCl_2$.

Table A.1. Bond distances (Å) for (*S*)-(xylyl-PHANEPHOS)$PtCl_2$.

Bond	Length(Å)	Bond	Length (Å)
Pt(1)-P(2)	2.2739(12)	C(19)-C(32)	1.499(8)
Pt(1)-P(1)	2.2749(12)	C(20)-C(21)	1.380(9)
Pt(1)-Cl(2)	2.3521(12)	C(21)-C(22)	1.388(8)
Pt(1)-Cl(1)	2.3630(13)	C(22)-C(23)	1.492(8)
P(1)-C(9)	1.827(5)	C(23)-C(24)	1.542(11)
P(1)-C(1)	1.831(6)	C(24)-C(25)	1.555(10)
P(1)-C(17)	1.844(5)	C(25)-C(26)	1.355(9)
P(2)-C(41)	1.834(5)	C(25)-C(30)	1.385(7)
P(2)-C(29)	1.839(6)	C(26)-C(27)	1.408(9)
P(2)-C(33)	1.842(5)	C(27)-C(28)	1.398(8)
C(1)-C(6)	1.396(9)	C(28)-C(29)	1.408(8)
C(1)-C(2)	1.423(9)	C(28)-C(31)	1.541(9)
C(2)-C(3)	1.446(10)	C(29)-C(30)	1.397(8)
C(3)-C(4)	1.338(13)	C(31)-C(32)	1.567(10)
C(3)-C(7)	1.504(14)	C(33)-C(38)	1.379(7)
C(4)-C(5)	1.452(15)	C(33)-C(34)	1.417(8)
C(5)-C(6)	1.403(10)	C(34)-C(35)	1.376(8)
C(5)-C(8)	1.533(12)	C(35)-C(36)	1.403(10)
C(9)-C(10)	1.391(8)	C(35)-C(39)	1.519(9)
C(9)-C(14)	1.395(9)	C(36)-C(37)	1.379(9)
C(10)-C(11)	1.381(9)	C(37)-C(38)	1.394(8)
C(11)-C(12)	1.367(10)	C(37)-C(40)	1.507(9)
C(11)-C(15)	1.551(10)	C(41)-C(46)	1.382(8)
C(12)-C(13)	1.402(10)	C(41)-C(42)	1.412(8)
C(13)-C(14)	1.404(8)	C(42)-C(43)	1.402(8)
C(13)-C(16)	1.504(10)	C(43)-C(44)	1.385(11)
C(17)-C(18)	1.394(7)	C(43)-C(47)	1.507(10)
C(17)-C(22)	1.423(7)	C(44)-C(45)	1.340(11)
C(18)-C(19)	1.400(8)	C(45)-C(46)	1.387(8)
C(19)-C(20)	1.387(9)	C(45)-C(48)	1.594(11)

Table A.2. Bond angles (°) for (*S*)-(xylyl-PHANEPHOS)$PtCl_2$.

Bonds	Angle (°)	Bonds	Angle (°)
P(2)-Pt(1)-P(1)	103.75(4)	C(23)-C(24)-C(25)	111.0(5)
P(2)-Pt(1)-Cl(2)	85.54(4)	C(26)-C(25)-C(30)	117.5(6)
P(1)-Pt(1)-Cl(2)	164.96(4)	C(26)-C(25)-C(24)	122.9(6)
P(2)-Pt(1)-Cl(1)	170.19(5)	C(30)-C(25)-C(24)	118.0(6)
P(1)-Pt(1)-Cl(1)	84.47(5)	C(25)-C(26)-C(27)	120.5(5)
Cl(2)-Pt(1)-Cl(1)	87.58(5)	C(28)-C(27)-C(26)	120.9(6)
C(9)-P(1)-C(1)	108.5(3)	C(27)-C(28)-C(29)	116.6(6)
C(9)-P(1)-C(17)	108.7(2)	C(27)-C(28)-C(31)	116.5(6)
C(1)-P(1)-C(17)	96.1(2)	C(29)-C(28)-C(31)	125.9(5)
C(9)-P(1)-Pt(1)	112.38(18)	C(30)-C(29)-C(28)	118.9(5)
C(1)-P(1)-Pt(1)	108.1(2)	C(30)-C(29)-P(2)	109.8(4)
C(17)-P(1)-Pt(1)	121.31(16)	C(28)-C(29)-P(2)	131.3(5)
C(41)-P(2)-C(29)	111.2(3)	C(25)-C(30)-C(29)	122.1(5)
C(41)-P(2)-C(33)	107.0(2)	C(28)-C(31)-C(32)	110.9(5)
C(29)-P(2)-C(33)	97.7(2)	C(19)-C(32)-C(31)	112.8(5)
C(41)-P(2)-Pt(1)	108.76(17)	C(38)-C(33)-C(34)	117.9(5)
C(29)-P(2)-Pt(1)	117.52(18)	C(20)-C(19)-C(32)	123.3(6)

C(33)-P(2)-Pt(1)	113.88(17)	C(18)-C(19)-C(32)	119.9(5)
C(6)-C(1)-C(2)	120.1(6)	C(21)-C(20)-C(19)	120.5(5)
C(6)-C(1)-P(1)	119.7(5)	C(20)-C(21)-C(22)	123.6(5)
C(2)-C(1)-P(1)	119.5(4)	C(21)-C(22)-C(17)	115.4(5)
C(1)-C(2)-C(3)	119.3(7)	C(21)-C(22)-C(23)	116.7(5)
C(4)-C(3)-C(2)	119.0(8)	C(17)-C(22)-C(23)	125.9(5)
C(4)-C(3)-C(7)	120.9(8)	C(22)-C(23)-C(24)	116.2(6)
C(2)-C(3)-C(7)	120.1(9)	C(38)-C(33)-P(2)	124.6(4)
C(3)-C(4)-C(5)	122.9(7)	C(34)-C(33)-P(2)	117.5(4)
C(6)-C(5)-C(4)	117.7(7)	C(35)-C(34)-C(33)	120.9(6)
C(6)-C(5)-C(8)	119.5(10)	C(34)-C(35)-C(36)	119.4(6)
C(4)-C(5)-C(8)	122.8(8)	C(34)-C(35)-C(39)	122.3(7)
C(1)-C(6)-C(5)	120.8(8)	C(36)-C(35)-C(39)	118.3(6)
C(10)-C(9)-C(14)	118.6(5)	C(37)-C(36)-C(35)	120.8(5)
C(10)-C(9)-P(1)	123.9(5)	C(36)-C(37)-C(38)	118.7(5)
C(14)-C(9)-P(1)	117.5(4)	C(36)-C(37)-C(40)	119.9(6)
C(11)-C(10)-C(9)	122.0(6)	C(38)-C(37)-C(40)	121.3(6)
C(12)-C(11)-C(10)	118.3(6)	C(33)-C(38)-C(37)	122.2(5)
C(12)-C(11)-C(15)	123.4(7)	C(46)-C(41)-C(42)	119.9(5)
C(10)-C(11)-C(15)	118.2(7)	C(46)-C(41)-P(2)	118.7(4)
C(11)-C(12)-C(13)	122.8(5)	C(42)-C(41)-P(2)	121.4(4)
C(12)-C(13)-C(14)	117.4(6)	C(43)-C(42)-C(41)	119.2(6)
C(12)-C(13)-C(16)	119.4(6)	C(44)-C(43)-C(42)	118.4(6)
C(14)-C(13)-C(16)	123.1(6)	C(44)-C(43)-C(47)	121.5(6)
C(9)-C(14)-C(13)	120.9(6)	C(42)-C(43)-C(47)	120.1(7)
C(18)-C(17)-C(22)	119.2(5)	C(45)-C(44)-C(43)	122.5(6)
C(18)-C(17)-P(1)	109.7(4)	C(44)-C(45)-C(46)	120.3(6)
C(22)-C(17)-P(1)	131.0(4)	C(44)-C(45)-C(48)	121.5(6)
C(17)-C(18)-C(19)	122.9(5)	C(46)-C(45)-C(48)	118.2(7)
C(20)-C(19)-C(18)	115.3(5)	C(41)-C(46)-C(45)	119.7(6)

Table A.3 Torsion angles (Å) for (*S*)-(xylyl-PHANEPHOS)$PtCl_2$.

Bonds	**Angle (°)**	**Bonds**	**Angle (°)**
P(2)-Pt(1)-P(1)-C(9)	124.0(2)	C(42)-C(41)-C(46)-C(45)	2.7(8)
Cl(2)-Pt(1)-P(1)-C(9)	-109.0(3)	P(2)-C(41)-C(46)-C(45)	-177.5(5)
Cl(1)-Pt(1)-P(1)-C(9)	-50.5(2)	C(44)-C(45)-C(46)-C(41)	-1.5(10)
P(2)-Pt(1)-P(1)-C(1)	-116.3(2)	C(48)-C(45)-C(46)-C(41)	-179.0(7)
Cl(2)-Pt(1)-P(1)-C(1)	10.7(3)	C(20)-C(21)-C(22)-C(23)	-153.6(6)
Cl(1)-Pt(1)-P(1)-C(1)	69.2(2)	C(18)-C(17)-C(22)-C(21)	-10.9(7)
P(2)-Pt(1)-P(1)-C(17)	-6.99(19)	P(1)-C(17)-C(22)-C(21)	170.8(4)
Cl(2)-Pt(1)-P(1)-C(17)	120.0(2)	C(18)-C(17)-C(22)-C(23)	152.6(6)
Cl(1)-Pt(1)-P(1)-C(17)	178.4(2)	P(1)-C(17)-C(22)-C(23)	-25.8(8)
P(1)-Pt(1)-P(2)-C(41)	111.46(17)	C(21)-C(22)-C(23)-C(24)	79.7(7)
Cl(2)-Pt(1)-P(2)-C(41)	-56.54(17)	C(17)-C(22)-C(23)-C(24)	-83.5(8)
Cl(1)-Pt(1)-P(2)-C(41)	-102.1(3)	C(22)-C(23)-C(24)-C(25)	6.2(8)
P(1)-Pt(1)-P(2)-C(29)	-16.0(2)	C(23)-C(24)-C(25)-C(26)	-88.2(7)
Cl(2)-Pt(1)-P(2)-C(29)	176.0(2)	C(23)-C(24)-C(25)-C(30)	76.9(7)
Cl(1)-Pt(1)-P(2)-C(29)	130.5(3)	C(30)-C(25)-C(26)-C(27)	-12.7(8)
P(1)-Pt(1)-P(2)-C(33)	-129.29(17)	C(24)-C(25)-C(26)-C(27)	152.5(6)
Cl(2)-Pt(1)-P(2)-C(33)	62.70(17)	C(25)-C(26)-C(27)-C(28)	-3.8(9)
Cl(1)-Pt(1)-P(2)-C(33)	17.1(4)	C(26)-C(27)-C(28)-C(29)	16.2(9)
C(9)-P(1)-C(1)-C(6)	-70.7(6)	C(26)-C(27)-C(28)-C(31)	-153.4(6)
C(17)-P(1)-C(1)-C(6)	41.4(6)	C(27)-C(28)-C(29)-C(30)	-12.1(8)
Pt(1)-P(1)-C(1)-C(6)	167.2(5)	C(31)-C(28)-C(29)-C(30)	156.4(6)

C(9)-P(1)-C(1)-C(2)	118.7(5)	C(27)-C(28)-C(29)-P(2)	170.9(5)
C(17)-P(1)-C(1)-C(2)	-129.2(5)	C(31)-C(28)-C(29)-P(2)	-20.5(10)
Pt(1)-P(1)-C(1)-C(2)	-3.4(6)	C(41)-P(2)-C(29)-C(30)	-177.4(4)
C(6)-C(1)-C(2)-C(3)	-2.0(11)	C(33)-P(2)-C(29)-C(30)	70.9(4)
P(1)-C(1)-C(2)-C(3)	168.6(6)	Pt(1)-P(2)-C(29)-C(30)	-51.2(4)
C(1)-C(2)-C(3)-C(4)	4.4(13)	C(41)-P(2)-C(29)-C(28)	-0.3(6)
C(1)-C(2)-C(3)-C(7)	-177.7(9)	C(33)-P(2)-C(29)-C(28)	-112.0(6)
C(2)-C(3)-C(4)-C(5)	-3.2(16)	Pt(1)-P(2)-C(29)-C(28)	126.0(5)
C(7)-C(3)-C(4)-C(5)	179.0(10)	C(26)-C(25)-C(30)-C(29)	16.9(8)
C(3)-C(4)-C(5)-C(6)	-0.4(15)	C(24)-C(25)-C(30)-C(29)	-149.1(6)
C(3)-C(4)-C(5)-C(8)	178.5(9)	C(28)-C(29)-C(30)-C(25)	-4.2(8)
C(2)-C(1)-C(6)-C(5)	-1.8(10)	P(2)-C(29)-C(30)-C(25)	173.3(4)
P(1)-C(1)-C(6)-C(5)	-172.3(6)	C(27)-C(28)-C(31)-C(32)	69.9(7)
C(4)-C(5)-C(6)-C(1)	3.0(11)	C(29)-C(28)-C(31)-C(32)	-98.7(7)
C(8)-C(5)-C(6)-C(1)	-175.9(7)	C(20)-C(19)-C(32)-C(31)	-103.5(7)
C(1)-P(1)-C(9)-C(10)	22.5(6)	C(18)-C(19)-C(32)-C(31)	61.8(8)
C(17)-P(1)-C(9)-C(10)	-80.9(5)	C(28)-C(31)-C(32)-C(19)	18.2(8)
Pt(1)-P(1)-C(9)-C(10)	142.0(4)	C(41)-P(2)-C(33)-C(38)	106.0(5)
C(1)-P(1)-C(9)-C(14)	-158.8(5)	C(29)-P(2)-C(33)-C(38)	-138.9(5)
C(17)-P(1)-C(9)-C(14)	97.8(5)	Pt(1)-P(2)-C(33)-C(38)	-14.2(5)
Pt(1)-P(1)-C(9)-C(14)	-39.3(5)	C(41)-P(2)-C(33)-C(34)	-74.4(4)
C(14)-C(9)-C(10)-C(11)	-2.0(9)	C(29)-P(2)-C(33)-C(34)	40.7(4)
P(1)-C(9)-C(10)-C(11)	176.6(5)	Pt(1)-P(2)-C(33)-C(34)	165.4(4)
C(9)-C(10)-C(11)-C(12)	0.0(9)	C(38)-C(33)-C(34)-C(35)	-0.9(8)
C(9)-C(10)-C(11)-C(15)	178.6(6)	P(2)-C(33)-C(34)-C(35)	179.5(5)
C(10)-C(11)-C(12)-C(13)	0.4(9)	C(33)-C(34)-C(35)-C(36)	0.0(10)
C(15)-C(11)-C(12)-C(13)	-178.1(6)	C(33)-C(34)-C(35)-C(39)	178.8(7)
C(11)-C(12)-C(13)-C(14)	1.2(9)	C(34)-C(35)-C(36)-C(37)	0.0(10)
C(11)-C(12)-C(13)-C(16)	177.2(7)	C(39)-C(35)-C(36)-C(37)	-178.9(7)
C(10)-C(9)-C(14)-C(13)	3.7(9)	C(35)-C(36)-C(37)-C(38)	0.9(9)
P(1)-C(9)-C(14)-C(13)	-175.0(4)	C(35)-C(36)-C(37)-C(40)	-176.4(7)
C(12)-C(13)-C(14)-C(9)	-3.3(9)	C(34)-C(33)-C(38)-C(37)	1.8(8)
C(16)-C(13)-C(14)-C(9)	-179.1(7)	P(2)-C(33)-C(38)-C(37)	-178.6(4)
C(9)-P(1)-C(17)-C(18)	172.7(4)	C(36)-C(37)-C(38)-C(33)	-1.8(8)
C(1)-P(1)-C(17)-C(18)	60.9(4)	C(40)-C(37)-C(38)-C(33)	175.4(6)
Pt(1)-P(1)-C(17)-C(18)	-54.7(4)	C(29)-P(2)-C(41)-C(46)	97.4(5)
C(9)-P(1)-C(17)-C(22)	-8.8(6)	C(33)-P(2)-C(41)-C(46)	-156.9(4)
C(1)-P(1)-C(17)-C(22)	-120.6(5)	Pt(1)-P(2)-C(41)-C(46)	-33.5(4)
Pt(1)-P(1)-C(17)-C(22)	123.8(4)	C(29)-P(2)-C(41)-C(42)	-82.7(5)
C(22)-C(17)-C(18)-C(19)	-3.2(8)	C(33)-P(2)-C(41)-C(42)	22.9(5)
P(1)-C(17)-C(18)-C(19)	175.5(4)	Pt(1)-P(2)-C(41)-C(42)	146.4(4)
C(17)-C(18)-C(19)-C(20)	16.8(8)	C(46)-C(41)-C(42)-C(43)	-0.3(8)
C(17)-C(18)-C(19)-C(32)	-149.6(6)	P(2)-C(41)-C(42)-C(43)	179.8(4)
C(18)-C(19)-C(20)-C(21)	-16.3(8)	C(41)-C(42)-C(43)-C(44)	-3.1(9)
C(32)-C(19)-C(20)-C(21)	149.6(6)	C(41)-C(42)-C(43)-C(47)	179.4(7)
C(19)-C(20)-C(21)-C(22)	2.5(10)	C(42)-C(43)-C(44)-C(45)	4.4(11)
C(20)-C(21)-C(22)-C(17)	11.4(9)	C(47)-C(43)-C(44)-C(45)	-178.2(8)
C(43)-C(44)-C(45)-C(48)	175.3(8)	C(43)-C(44)-C(45)-C(46)	-2.1(12)

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