PALLADIUM-CATALYZED ASYMMETRIC ALLYLIC ALKYLATION: INSIGHTS, APPLICATION TOWARD CYCLOPENTANOID AND CYCLOHEPTANOID MOLECULES, AND THE TOTAL SYNTHESIS OF SEVERAL DAUCANE SESQUITERPENES

Thesis by

Nathan Bruce Bennett

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To my wife,
Chanel, and
my son, Eli

ACKNOWLEDGEMENTS

Brian frequently refers to the graduate school experience as “a marathon and not a sprint.” While this sentiment expresses the exhaustive nature of the effort that necessitates pacing oneself, the metaphor also suggests a reward is achieved upon completion of the task. Ultimately, my graduate experience has been immensely rewarding, and one of the greatest aspects of that is finally seeing my last five years of work condensed into this volume. Gratefully, the “race” that encompasses this pursuit was not run alone and I have many to thank for inspiring, encouraging, and helping me to attain my doctorate.

First, I would like to thank Brian Stoltz for being my advisor. When I was accepted to Caltech, Brian allowed me to begin my research early, before classes started in the fall. This arrangement was made with the understanding that I may ultimately join another lab. I have always been very grateful to him for supporting me as I adjusted to graduate life over that summer, since I know this time was more beneficial for me than for him. Close to the end of my graduate experience, Brian also arranged postgraduate funding for me before my postdoc was set to begin. I really appreciate how he has helped me provide for my family.

In the lab, Brian has granted a fair amount of flexibility on my projects, encouraging me to focus on the problems I found exciting and to even explore reactions outside of my main pursuits. This freedom has allowed me to try a variety of transformations and learn multiple techniques. In these efforts, Brian has provided numerous ideas on how to overcome difficult obstacles, and I quickly learned that the reactions he suggests almost always work and usually helped me get past the problem I

was facing. I also enjoyed the time I spent in his office crafting my research into the outline of a paper, working side by side as everything came together.

Brian is also an excellent instructor. I have had the privilege to not only take a class from him, but have also served as his teaching assistant while he lectured the undergraduate organic series. He teaches his courses with great depth and clarity, and I know his students appreciate him.

My committee members have also been very helpful during my time at Caltech. Professor Sarah Reisman began teaching at Caltech at the start of my program, and we incidentally had our sons around the same time. From a number of experiences, I have come to think of Sarah as a friend. She has been especially supportive over the last few months and has served as somewhat of a surrogate advisor while Brian has been away. Sarah has offered a lot of advice on my most recent research, and I am particularly appreciative of her insight into samarium diiodide reductions. Most importantly, I am very grateful for her willingness to have acted as my committee chairman.

Professor Linda Hsieh-Wilson is kind and has provided helpful suggestions at my yearly committee meetings. In my third year meeting, she gave me some of the best advice that I have received while at Caltech with regards to the direction of my project.

Dr. Scott Virgil has an expansive knowledge of chemistry and will find an answer to any question you have. In addition to serving on my committee, Scott has assisted me in the laboratory on numerous occasions. The high-throughput screen that is discussed in Chapter 1 of my thesis would not have been realized without him. I would also like to thank Scott for his help with a difficult hydrogenation I had in my daucane sesquiterpene project. His wife, Silva, has also been extremely kind to my family and me. We had a

wonderful time at their home one evening and enjoy seeing her at department and holiday parties. They are warm and generous people that I am so happy to have come to know.

I ambushed Professor Greg Fu to ask him to be the final member of my committee while he was visiting from MIT for a recruiting weekend prior to his move to Caltech. He had never met me before, but did not hesitate to accept. I am grateful for the time he has taken to offer advice on my research, proposals, and a publication we were preparing for submission.

While at Caltech, I have been blessed to work with numerous graduate students and postdocs. When I began my graduate studies, we were located in the Crellin building and my first baymate was Jenn Stockdill. As I was a young and inexperienced graduate student, Jenn taught me a lot of laboratory techniques and helped me set up my first LDA reaction; I have since run many. I credit Jenn for introducing me to "Wait, Wait Don't Tell Me" and Billy Joel, both of which I now listen to frequently. Jenn is currently a professor at Wayne State University and I wish her the best.

With our move to the Schlinger laboratory, I shared a hood with Allen Hong. Allen is a persistent and detail-oriented scientist. He is always positive, even when things are not going as expected. We have worked on several projects together that have resulted in a number of publications; our joint efforts encompass Chapter 2 of my thesis. Allen is now a postdoc at UC Irvine with Prof. Chris Vanderwal. When Brian heard that we would both be moving to Irvine for our postdocs, he jokingly suggested that we find some way to continue our collaborative efforts. I am really grateful for Allen's friendship and for all of the projects we have worked on together.

I have had a number of other baymates over the last five years. Dr. Chris Henry taught me a lot about laboratory technique and NMR analysis. He likely looked at every spectra during my first year and helped me figure out coupling constants on several occasions. I am grateful for his friendship in the lab and on the basketball court. Nat Sherden taught me so much about the mechanistic aspects of the Tsuji allylation and Futurama. Max Loewinger is a good friend with an infectious excitement for chemistry. Seojung Han is one of the most diligent chemists I have met. Dr. Wen-Bo (Boger) Liu was a great collaborator on the allylic alkylation research; our joint work is discussed in Chapter 1 of my thesis. I also appreciate all of the things he has proofread for me.

Chris Gilmore and Pam Tadross became great friends to my wife and I. Chris and his hoodmate, Dr. Florian Vogt, kept things lively in our bay. Flo instituted weekly Queen and ABBA nights, and I credit him for my interest in classic music. Between the two, there was always an interesting conversation or podcast coming from their hood. Although not my baymate, Pam was particularly helpful in sculpting my development as a chemist. She read almost everything I wrote before she graduated, and I always appreciated her straightforward comments and insights. She will make an excellent professor one day because she cares about others and works tirelessly to see them succeed. I appreciate how Pam and Chris always talked with my wife at group parties and kept her involved, and how they were so excited for the birth of our son. We are so happy they found each other and got married. It was also great to meet Chris' parents upon their move to Pasadena. They are awesome people, and we've enjoyed visiting with them at their home and various group parties.

Thomas Jensen is one of the best examples of an organic chemist I have seen. He set up so many reactions on a daily basis and was extremely diligent at getting things done. I remember one day when his hoodmate thought he had run more reactions than Thomas only to discover Thomas had actually set up a robotic screen that crushed the hoodmate's number. My goal everyday was to strive to be a little more like Thomas.

The research presented in Chapter 1 was performed in conjunction with Doug Duquette. While I wrote the paper, Doug finished collecting the laboratory data we needed. I was really impressed with how quickly he took care of everything and how fast we got that paper out. Doug is a great scientist and I am happy to have worked with him. I am also grateful to Drs. Jimin Kim, Wen-Bo (Boger) Liu, Alex Marziale, and Doug Behenna for contributing to these efforts.

Although not discussed in my thesis, I recently began working with Kelvin Bates on a collaborative project with Professors Paul Wennberg and John Seinfeld where we are making compounds that are hypothesized to exist in the atmosphere. Kelvin had no prior synthesis experience, but he has learned quickly and I know he will do well.

There have been many people in our lab during my time here. In my year, Alex Goldberg, Jonny Gordon, and Boram Hong have been great. Early on, Alex, Jonny, and I played basketball weekly. A number of students who preceded me had good advice and helped in my development including Mike Krout, Kevin Allan, and John Enquist. I know that I have inevitably neglected many that I have interacted with, and I greatly apologize for this. So many have contributed to my graduate experience, and it has been a great pleasure to work with my fellow Stoltz group members.

I must also thank several others for editing my proposals and thesis. Doug Duquette, Christopher Haley, Dr. Alex Marziale, Nick O'Connor, Gloria Sheng, and Ximena De Silva Tavares Bongoll each read one of my proposals. They provided invaluable perspective on the chemistry I proposed and caught all of the mistakes I made. I am also extremely grateful to Jeff Holder, Kelly Kim, Katerina Korch, Dr. Wen-Bo (Boger) Liu, Yiyang Liu, Nick O'Connor, and Beau Pritchett for reading and editing portions of my thesis.

In addition to the awesome students and postdocs at Caltech, we have the highest quality of staff. Agnes Tong is very understanding and really takes the time to listen. She was always willing to work out teaching assignments and other things to accommodate my schedule. Agnes does so much for the department and still finds time to care about each of the students individually. This is extremely challenging, but she juggles it all beautifully.

On the scientific side, Dr. David VanderVelde has helped me obtain and analyze numerous NMR spectra. He has taught me a lot about the experiments that are available and showed me how to run and interpret them. I really enjoyed the variable temperature experiment we performed to resolve atropisomers that is discussed in Chapter 2. Dr. Mona Shahgoli and Naseem Torian have provided a mass for every compound that I submitted. This has often proved somewhat challenging, as many of the molecules I made toward daucene are greasy and hard to ionize.

Assistant Dean Natalie Gilmore has also been amazing and has helped my family immensely. She listened to our needs, especially as we were preparing for the birth of

our son, and has helped us in so many ways. We are indebted to her for her many kindnesses, especially for my appointment as an ARCS foundation scholar.

The ARCS foundation is a wonderful organization that recognizes and supports both undergraduate and graduate students who are pursuing degrees in science. My wife and I are so grateful for the fellowship they provided us. I have always enjoyed meeting with the different members during our yearly luncheon. They are kind people who care about our country's future and are striving to promote American innovation by funding scientific research.

I would not have arrived at Caltech without the guidance and direction of several professors from my undergraduate experience. The most influential of these was Prof. Steven Fleming. I worked for "Doc" during my junior and senior years performing research on a photochemical rearrangement. Doc believes in his students and pushes them to be their best. He met with us late in the evening every week where we went through countless organic chemistry problems. I learned so much from these sessions and from his physical organic chemistry course. Ultimately, Doc taught me to think like an organic chemist. Our weekly group meetings and the parties at his home are some of the best memories from my time at BYU.

While at BYU, I also performed research jointly under Professors Noel Owen and Steven Wood. Dr. Owen took a chance accepting me into his lab since my only previous interaction with him had been as a student in a religion class he taught. My time spent isolating bioactive metabolites from plant endophytes contributed greatly to my interest in the total synthesis of natural products. One of the experiences I enjoyed with Professor

Wood was the trip that several students and I took with him to an ACS regional meeting in Nevada where we presented a poster on our research.

Although I never performed research in his lab, I am also deeply indebted to Professor Steven Castle. Professor Castle taught my advanced organic chemistry laboratory course, which helped cement my desire to pursue graduate studies in organic synthesis. I learned to solve and love NMR problems in this class, and to this day, 2D NMR spectra are one of my favorite aspects of research. I also served as a teaching assistant to Dr. Castle for the same course and learned a lot under his guidance. I am especially grateful for the many times he has written letters of recommendation on my behalf.

Finally and most importantly, I would like to thank my family. My parents have been so supportive of my education. When I was little, my mother and father set a wonderful example on the importance of learning and pushed me to perform. I loved school and wanted to do well because of them. I remember my mother staying up with me in fifth grade to help finish my state report the night before it was due. In high school, she taught me how to write and edited all of my papers. While growing up, my father helped me figure out math and science. I appreciated how he would discuss with me what college classes I should take. His guidance on my career has been so helpful. I am so grateful for their interest in my undergraduate education and that they encouraged me to pursue my doctorate. Chanel's family has been equally supportive and accepted me as one of their own from the start. They have kept me well fed and provided numerous sweets. I love being in their home and have so many memories from time spent there.

I first met my wife, Chanel, at the beginning of my graduate studies and we were married shortly thereafter. It was good we met when we did, as I do not know how I would have gotten through everything without her. The timing of our meeting and courtship likely helped her deal with my long hours in the lab since this is the only life we have known together. She is a fabulous wife and mother. Our son, Eli, is so much fun. I love how he would wave and say, "bye-bye" from the front door as I headed off to the lab every morning, and I was always so happy to see his smiling face when I returned. I love them both so much and am so grateful for their love and support.

ABSTRACT

The asymmetric construction of quaternary stereocenters is a topic of great interest in the organic chemistry community given their prevalence in natural products and biologically active molecules. Over the last decade, the Stoltz group has pursued the synthesis of this challenging motif via a palladium-catalyzed allylic alkylation using chiral phosphinooxazoline (PHOX) ligands. Recent results indicate that the alkylation of lactams and imides consistently proceeds with enantioselectivities substantially higher than any other substrate class previously examined in this system. This observation prompted exploration of the characteristics that distinguish these molecules as superior alkylation substrates, resulting in newfound insights and marked improvements in the allylic alkylation of carbocyclic compounds.

General routes to cyclopentanoid and cycloheptanoid core structures have been developed that incorporate the palladium-catalyzed allylic alkylation as a key transformation. The unique reactivity of α-quaternary vinylogous esters upon addition of hydride or organometallic reagents enables divergent access to γ-quaternary acylcyclopentenes or cycloheptenones through respective ring contraction or carbonyl transposition pathways. Derivatization of the resulting molecules provides a series of mono-, bi-, and tricyclic systems that can serve as valuable intermediates for the total synthesis of complex natural products.

The allylic alkylation and ring contraction methodology has been employed to prepare variably functionalized bicyclo[5.3.0]decane molecules and enables the enantioselective total syntheses of daucene, daucenal, epoxydaucenal B, and 14-*p*-anisoyloxydauc-4,8-diene. This route overcomes the challenge of accessing β-substituted acylcyclopentenes by employing a siloxyenone to effect the Grignard addition and ring opening in a single step. Subsequent ring-closing metathesis and aldol reactions form the hydroazulene core of these targets. Derivatization of a key enone intermediate allows access to either the daucane sesquiterpene or sphenobolane diterpene carbon skeletons, as well as other oxygenated scaffolds.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
p-ABSA	*para*-acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BHT	2,6-di-*tert*-butyl-4-methylphenol ("butylated hydroxytoluene")
BINAP	(1,1'-binaphthalene-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
i-Bu	*iso*-butyl
n-Bu	butyl or *norm*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl

c	concentration of sample for measurement of optical rotation
^{13}C	carbon-13 isotope
^{14}C	carbon-14 isotope
/C	supported on activated carbon charcoal
°C	degrees Celcius
calc'd	calculated
CAN	ceric ammonium nitrate
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: *confer*)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
d	dextrorotatory
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBDMH	*N,N*'-dibromo-5,5-dimethylhydantoin

DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexyl carbodiimide
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
de	diastereomeric excess
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutyl aluminum hydride
DMA	dimethylacetamide
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess–Martin periodinane (1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one)
DMSO	dimethylsulfoxide
DMTS	dimethylthexylsilyl
DPPA	diphenylphosphorylazide
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
DTT	dithiothreitol
ee	enantiomeric excess
E	methyl carboxylate (CO_2CH_3)
E^+	electrophile

E	trans (entgegen) olefin geometry
EDCI	*N*-(3-Dimethylaminopropyl)-*N*-2-ethylcarbodiimide hydrochloride
e.g.	for example (Latin: *exempli gratia*)
EI	electron impact
eq	equation
equiv	equivalent(s)
ESI	electrospray ionization
Et	ethyl
et al.	and others (Latin: *et alii*)
FAB	fast atom bombardment
Fmoc	fluorenylmethyloxycarbonyl
g	gram(s)
h	hour(s)
^{1}H	proton
^{2}H	deuterium
^{3}H	tritium
[H]	reduction
HATU	2-(7-aza-1*H*-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HMDS	hexamethyldisilamide or hexamethyldisilazide
HMPT	hexamethylphosphoramide
$h\nu$	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry

Hz	hertz
IBX	2-iodoxybenzoic acid
IC_{50}	half maximal inhibitory concentration (50%)
i.e.	that is (Latin: *id est*)
IR	infrared spectroscopy
J	coupling constant
k	rate constant
kcal	kilocalorie(s)
kg	kilogram(s)
KHMDS	potassium bis(trimethylsilyl)amide
L	liter or neutral ligand
l	levorotatory
LA	Lewis acid
LD_{50}	median lethal dose (50%)
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LICA	lithium isopropylcyclohexylamide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion
m	meta
µ	micro
m-CPBA	*meta*-chloroperbenzoic acid

Me	methyl
mg	milligram(s)
MHz	megahertz
MIC	minimum inhibitory concentration
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular seives
m/*z*	mass-to-charge ratio
N	normal or molar
NBS	*N*-bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu^-	nucleophile
o	ortho
[O]	oxidation
t-Oct	*tert*-octyl (1,1,3,3-tetramethylbutyl)

p	para
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
Piv	pivalate
pK_a	acid dissociation constant
PKS	polyketide synthase
PMB	*para*-methoxybenzyl
pmdba	bis(4-methoxybenzylidene)acetone
ppm	parts per million
PPTS	pyridinium *para*-toluenesulfonate
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl or *norm*-propyl
psi	pounds per square inch
py	pyridine
q	quartet
R	alkyl group
R	rectus
RCM	ring-closing metathesis
REDAL	sodium bis(2-methoxyethoxy)aluminum hydride
ref.	reference

R_f	retention factor
s	singlet or seconds
S	sinister
sat.	saturated
SEM	2-(trimethylsilyl)ethoxymethyl
SOD	superoxide dismutase
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAT	tetra-*n*-butylammonium difluorotriphenylsilicate
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TCA	trichloroacetic acid
temp	temperature
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
THIQ	tetrahydroisoquinoline
TIPS	triisopropylsilyl
TLC	thin layer chromatography

TMEDA	*N*,*N*,*N'*,*N'*-tetramethylethylenediamine
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TOF	time-of-flight
tol	tolyl
Tr	triphenylmethane (trityl)
Troc	2,2,2-trichloroethoxycarbonyl
Ts	*para*-toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry