

STRATEGIES FOR THE STEREOSELECTIVE SYNTHESIS OF CARBON
QUATERNARY CENTERS VIA TRANSITION METAL-CATALYZED
ALKYLATION OF ENOLATE COMPOUNDS

Thesis by
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*To Debbie Elaine Ehlers,
My mom.*

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All of this started with a car accident. A bad car accident. After spending a week in the hospital, and undergoing a few surgeries, I had a salvaged hand and a tremendous impression of my surgeon, Dr. Michael Mara. I was so impressed, in fact, that I decided to go to college with the intention of one day going to medical school. So, I'd like to start by thanking him.

During his office hour for sophomore organic chemistry, I asked Prof. Tristan Lambert how it was that electrons passed through a nodal plane during an S_N2 displacement if the nodal plane is defined as a space in which there is zero electron density. Years later, Tristan would tell me that at this point he thought, "who is this surfer...is he serious?" For introducing me to organic chemistry, for being my first mentor in chemistry, for taking me into his lab, for always being supportive, for giving me my own project after just a month of tutelage, for teaching me the value inherent in and process of the scientific method, for steering me away from medical school and encouraging me to pursue the graduate education in chemistry that I have now nearly completed, I offer a heartfelt thank you to Tristan. I am also indebted to all of the people who populated the Lambert lab during my tenure there. In particular, Ethan Fisher, my mentor, who is a very talented teacher and chemist, and who was extremely patient with me as I learned the basics of laboratory chemistry. Thank you, as well, to Rocky, Brendan, Julia, Bandar, Elnaz, Tim, and Lisa all of whom were excellent labmates and friends and made the Lambert lab a fun and highly educational place.

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My doctoral advisor, Prof. Brian Stoltz, is truly the best boss one could hope to have and I owe the lion's share of my development as a scientist to him. In research, Brian is unfailingly patient, encouraging, didactic, enthusiastic, and lighthearted. He gave me the freedom to try a bunch of ideas that were longshots at best, the freedom to fail in trying, and the guidance to learn from my failure. He pushed me when I needed to be pushed, and always acted in my best interest. His ability to consolidate the best

interest of the individual and the best interest of the group is truly admirable. I have learned so much from Brian not only in chemistry, but also with respect to being a leader, being a good educator, being a professional colleague, and being a generally good scientist. On a personal level, Brian has been an incredibly understanding and dependable. I've walked into his office on countless occasions and completely blindsided him with an unexpected, non-science conversation to which he has, without fail, stopped what he was doing and listened. And through this all, he has been respectful, supportive and amiable. He has become one of my foremost role models, and with a heavy heart I will leave his lab and try my best to emulate his manner of engaging in science and in my profession life.

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conducted in my time in the Stoltz lab built on discoveries he made years ago. Beyond all of that Big Doug is a great leader and a thoughtful friend.

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In the spring of 2010, Robert Allen Craig II, and myself beat Sarah Reisman and Roger Nani in a game of beerpong, at which point Sarah was obliged to do a kegstand. And I took a picture of her doing it. This may have been the moment I decided to come to Caltech. Since orientation and the G0 days, Rob Craig has been a great friend and colleague. We went through classes together, TA'd chem1A together and started out in the Stoltz lab together. This series of events that would have been considerably more dull, depressing and challenging, respectively, had it not been for that tall, loveable, goofball that was born Mr. Baby. Tiny Mr. Baby has been an invaluable compatriot and companion throughout graduate school. One who pushed me to work way too late into the evening and was pushed back for years. Who was

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During the first couple of years of research, in particular, I was quite often a very tired, frustrated version of myself, and I certainly would not have made it to this point without the support of friends and family outside of the lab. To the closest thing the Stoltz lab has to an honorary member, John Steeves, a huge thanks. Sleeve has become a very close friend during the last five years and his patience for my blathering on about chemistry on the way to or from surfing, his patience in painstakingly explaining his own research to me on the way to or from surfing, his companionship during late nights in Sherman Fairchild Library, his enthusiasm for Frisbee golf and generally cheerful comportment have all been indispensable. Sleeve is very much the embodiment of a good-natured Canadian. As a case in point: he didn't complain after getting hit in the face with a surfboard, or when the doctor sewing him back together

from said incident remarked that the inside of his mouth “looked like hamburger meat” for the third time. I have for years been quietly, if slowly, learning to be a more good-natured, thoughtful and considerate person by following his example.

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The Stoltz lab really has become like a home to me. I feel at home at my hood, and at home at my desk. That is a pretty amazing thing to be able to say and it stems from the general air about the lab, which arises from the people who show up day after day to populate it. To every member of the Stoltz group past and present who has done so – thank you for making the group the welcoming, exciting, engaging, enlightening, fun place that is. To the very capable younger members of the lab that will carry it into the future, I am confident that you will keep that up. Brian says that his goal is for the Stoltz lab to be the best synthetic chemistry lab in the world: in my opinion, it very much is.

– *Corey M. Reeves, April 29th, 2015*

ABSTRACT

Notwithstanding advances in modern chemical methods, the selective installation of sterically encumbered carbon stereocenters, in particular all-carbon quaternary centers, remains an unsolved problem in organic chemistry. The prevalence of all-carbon quaternary centers in biologically active natural products and pharmaceutical compounds provides a strong impetus to address current limitations in the state of the art of their generation. This thesis presents four related projects, all of which share in the goal of constructing highly-congested carbon centers in a stereoselective manner, and in the use of transition-metal catalyzed alkylation as a means to address that goal.

The first research described is an extension of allylic alkylation methodology previously developed in the Stoltz group to small, strained rings. This research constitutes the first transition metal-catalyzed enantioselective α -alkylation of cyclobutanones. Under Pd-catalysis, this chemistry affords all-carbon α -quaternary cyclobutanones in good to excellent yields and enantioselectivities.

Next is described our development of a (trimethylsilyl)ethyl β -ketoester class of enolate precursors, and their application in palladium-catalyzed asymmetric allylic alkylation to yield a variety of α -quaternary ketones and lactams. Independent coupling partner synthesis engenders enhanced allyl substrate scope relative to allyl β -ketoester substrates; highly functionalized α -quaternary ketones generated by the union of our fluoride-triggered β -ketoesters and sensitive allylic alkylation coupling partners serve to demonstrate the utility of this method for complex fragment coupling.

Lastly, our development of an Ir-catalyzed asymmetric allylic alkylation of cyclic β -ketoesters to afford highly congested, vicinal stereocenters comprised of tertiary and all-carbon quaternary centers with outstanding regio-, diastereo-, and enantiocontrol is detailed. Implementation of a subsequent Pd-catalyzed alkylation affords dialkylated products with pinpoint stereochemical control of both chiral centers. The chemistry is then extended to include acyclic β -ketoesters and similar levels of selective and functional group tolerance are observed. Critical to the successful development of this method was the employment of iridium catalysis in concert with *N*-aryl-phosphoramidite ligands.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	angle of optical rotation of plane-polarized light
Å	angstrom(s)
<i>p</i> -ABSA	<i>para</i> -acetamidobenzenesulfonyl azide
Ac	acetyl
AIBN	azobisisobutyronitrile
APCI	atmospheric pressure chemical ionization
app	apparent
aq	aqueous
Ar	aryl group
At	benztriazolyl
atm	atmosphere(s)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
bp	boiling point
br	broad
Bu	butyl
<i>n</i> -Bu	butyl or <i>norm</i> -butyl
<i>t</i> -Bu	<i>tert</i> -butyl
Bz	benzoyl
<i>c</i>	concentration of sample for measurement of optical rotation

^{13}C	carbon-13 isotope
/C	supported on activated carbon charcoal
$^{\circ}\text{C}$	degrees Celcius
ca.	approximately (Latin: <i>circum</i>)
calc'd	calculated
Cbz	benzyloxycarbonyl
CCDC	Cambridge Crystallographic Data Centre
CDI	1,1'-carbonyldiimidazole
cf.	consult or compare to (Latin: <i>confer</i>)
cm^{-1}	wavenumber(s)
cod	1,5-cyclooctadiene
comp	complex
conc.	concentrated
Cy	cyclohexyl
CSA	camphor sulfonic acid
d	doublet
<i>d</i>	dextrorotatory
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
<i>de</i>	diastereomeric excess
DIAD	diisopropyl azodicarboxylate

DIBAL	diisobutyl aluminum hydride
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethylsulfoxide
dppb	1,3-bis(diphenylphosphino)butane
dppf	1,3-bis(diphenylphosphino)ferrocene
dppe	1,3-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphino)propane
dr	diastereomeric ratio
<i>ee</i>	enantiomeric excess
E	methyl carboxylate (CO ₂ CH ₃)
E ⁺	electrophile
<i>E</i>	trans (entgegen) olefin geometry
e.g.	for example (Latin: <i>exempli gratia</i>)
EI	electron impact
eq	equation
ESI	electrospray ionization
Et	ethyl
<i>et al.</i>	and others (Latin: <i>et alii</i>)
EtOAc	ethyl acetate
FAB	fast atom bombardment
g	gram(s)

h	hour(s)
^1H	proton
$h\nu$	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: <i>id est</i>)
iNOS	human-inducible nitric oxide synthase
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
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
LTMP	lithium 2,2,6,6-tetramethylpiperidide
m	multiplet or meter(s)
M	molar or molecular ion

<i>m</i>	meta
μ	micro
<i>m</i> -CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
MM	mixed method
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl (mesyl)
MS	molecular sieves
<i>m/z</i>	mass-to-charge ratio
N	normal or molar
NBS	<i>N</i> -bromosuccinimide
nm	nanometer(s)
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser effect
NOESY	nuclear Overhauser enhancement spectroscopy
Nu ⁻	nucleophile
<i>o</i>	ortho

[O]	oxidation
OAc	Acetate
<i>p</i>	para
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
pK_a	acid dissociation constant
PMB	<i>para</i> -methoxybenzyl
ppm	parts per million
Pr	propyl
<i>i</i> -Pr	isopropyl
py	pyridine
q	quartet
R	alkyl group
<i>R</i>	rectus
RCM	ring-closing metathesis
ref	reference
R_f	retention factor
RNA	ribonucleic acid
s	singlet or seconds
<i>S</i>	sinister
sat.	saturated
Selectfluor	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)

SFC	supercritical fluid chromatography
t	triplet
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBAT	tetra- <i>n</i> -butylammonium difluorotriphenylsilicate
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBHP	<i>tert</i> -butyl hydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
temp	temperature
Tf	trifluoromethanesulfonyl
t _R	retention time
THF	tetrahydrofuran
TLC	thin layer chromatography
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
TMSE	2(trimethylsilyl)ethyl
TOF	time-of-flight
tol	tolyl
Ts	<i>para</i> -toluenesulfonyl (tosyl)
UV	ultraviolet
w/v	weight per volume
v/v	volume per volume
X	anionic ligand or halide
Z	cis (zusammen) olefin geometry