THE DESIGN AND DEVELOPMENT OF PALLADIUM-CATALYZED AEROBIC OXIDATIVE TRANSFORMATIONS

Thesis by

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To my parents

ACKNOWLEDGMENTS

I should have written this days ago. "No," I kept telling myself. "Save it for the end. You should end on the acknowledgments." And now here I am, late to turn this thing in, rushing. But it's important to get this right. This is the part that everyone reads. Sure, there's the person who wants to look up this specific reference or that similar procedure, but come on, it's this, followed by the remark, "It seems kinda long."

I have to first thank Professor Brian Stoltz for his support, guidance, and enthusiasm. For an assistant professor to take on so many responsibilities and put forth such a tremendous effort in everything he does is truly remarkable. I appreciate the personal interactions I have had with him over the years, both as a mentor and as a friend. I've been thankful for his continuous interest in science, and for allowing me to forge my own research path with a pretty long leash. I've learned so much from him and his advice, and he has really provided me with an excellent model of what an advisor should be. I also want to thank his wife Erna for her supportive discussions during my time here.

I also want to thank the other members of my thesis committee at Caltech– Professor Robert Grubbs, Professor John Bercaw, and Professor Jonas Peters. I am extremely grateful for the time they have put into looking over my works during both the candidacy phase and the defense phase. Their insightful comments have been useful over the years in helping me develop my intuition as a scientist, and I appreciate the support that has been given to me through their efforts.

I want to express my gratitude for the opportunity I had at MIT. Steve Buchwald allowed me to work in his lab even though I was pretty much a total flake at the time. In hindsight, I really do wish I had taken better advantage of that chance than I did at the time, but I still learned a ton while there in spite of myself. Learning from Rob Singer and Dan Appella was an incredible experience, and I have an immense amount of appreciation for their efforts and their patience. My experience in the Buchwald lab allowed me to come to Caltech and be able jump right in without excessive orientation.

There have been a number of people in the Stoltz Group who have been involved in the palladium(II) project: Jeff Bagdanoff, Raissa Trend, Yeeman Ramtohul, Haiming

Zhang, Dave Ebner, Dan Caspi, Ryan McFadden, Toyoki Nishimata, and JT Mohr. Although I never worked directly with anyone at any given time on this project, I know this project would be nothing without all of their efforts. Jeff has done an excellent job in developing the oxidative kinetic resolution beyond the initial work. Raissa has done some of the most profound work on the palladium chemistry while I've been here. I have a great deal of respect for her skills in experimental design and execution. Haiming came in and cranked on the C-H bond functionalization chemistry. God, he runs a ton of reactions. I love that. I think his efforts have really helped to outline where the project needs to go in the future. Dave and Toyoki have both started working on non-sparteine-based systems. I'm happy to see that people are excited about taking the chemistry in this direction, despite how difficult it may be, and I wish them the best. I really admire their willingness to work on projects that can be challenging, but could eventually lead to some thrilling outcomes. I think that although there's still a bunch to be done, the project has come a long way in a pretty short amount of time. I have tried to point out their specific contributions in the text of the thesis, but I wanted to thank them collectively here as well.

I've had three baymates while in the group. Sarah Spessard was the first back in the days of 264 Crellin. I enjoyed playing tennis a bunch with Sarah Spessard in the early days. Though she kicked my butt most of the time, it helped to release some of the built up tension from the day-to-day lab stuff. In 204 Church, I then had the luxury (yes, that's the right word) of working next to Richmond Sarpong. I could have done with less Steely Dan or Hall & Oates, but he was an excellent coworker. His enthusiasm about chemistry was contagious, and I thoroughly enjoyed the scientific discussions we had in the years he was here. I hope he does great as a professor at Berkeley; I can't think of anyone more deserving of success. Mike Krout has been my baymate for almost a year. Although we haven't had too much time to work next to each other, it's been a pleasure working near him. I'm also grateful to him for putting up with way more Sonic Youth than he should have felt obligated to.

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has been fun to talk to, vent to, complain about the Sacramento Kings to, etc. He knows a boatload of information and could always answer even my most mundane questions. I've always appreciated the level-headedness of Jeremy May. He seems to have such a reasonable and healthy perspective on things that I've found refreshing and helpful toward achieving my own version of rationality. Jenn Stockdill is always good for an ice cream break or hanging out with Sage and Lily. JT Mohr has been great to talk to about music, the Daily Show, or heck, chemistry. I want to thank the following for their insightful assistance with drafts of this thesis (and proposals, for that matter): JT, Eric A., Mike K., Raissa, Haiming, Jeremy, Jenn, and Dave. Finally, I want to thank the Stoltz Group as a whole for creating an environment always willing to discuss science in an engaging manner. It's this environment that allows the lab to be successful as it has been, and I'm sure that the success will continue for years to come.

I have to single out Mike Meyer for a second. First, he's a San Francisco Giants fan (big plus). Second, he's really the only person that I've worked with on a project at the same time. Although none of it is appearing in this thesis (okay, one reaction), it has been a true pleasure to have the opportunity to work with him for the past few months. I've really admired his excitement about chemistry and his eagerness to learn and then perform. His willingness to get things done quickly helped to push this project along, and I'm certain his optimism and enthusiasm will carry this project to the end. I just want to thank him for having a huge part in helping to restore my excitement about chemistry after a particularly discouraging stretch (Chapter 5, *vide infra*).

Caltech is a unique place in that people can be incredibly interactive with one another across research groups in both scientific and social manners. I've frequently enjoyed being able to talk to people in other areas of the Caltech community about science or about anything else. Rather than go into detail about each one, which would take way too long, I'll just list them here. Joel Austin (Scrabble rocks), Andrew Waltman, Erin Guidry, Ian Mangion, Jon Owen, Julie Park, Arnab Chatterjee, Vy Dong, Nick Paras, Connie Lu, Steve Brown, Ted Betley, and Lori Lee. I appreciated the occasional discussions with all of them about whatever was on our minds. Tehshik Yoon was immensely helpful in the first couple of years I was here. I think he gets a lot of appreciation for his selfless impact in the MacMillan Group, but he was also able to

provide assistance outside of his own group. I want to make sure he and the rest of MacMillan's first batch of students are acknowledged for helping our group get off the ground in those early days. I also had several interesting discussions with Jen Love, for which I am exceptionally grateful. I have enjoyed the countless stimulating conversations with her in the halls, and I have an inordinate amount of respect for her as a scientist and as a friend.

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I need to thank the folks at anarchy@mit.edu. (No, we aren't anarchists.) The philosophical discussions, battle raps, and indie elitist posturing were incredibly entertaining and a frequently welcome distraction to work. Just names again: Mike Salamina, Mike Dewberry, Andy Stein, Ian Ross, Mike Perry, Jordan Gilliland, Mike O'Hara, Ian McCreery, Andy Kuziemko and Dan Amano.

Lastly, I need to thank my family for their continued support. Andrea and Henry have been hosting awesome Thanksgivings for many years now, and I've always enjoyed the chance to get away, even if only for a day, to visit with them. My parents have been continually supportive of me in helping me reach my goals. I think as I've gotten older, I've become more aware of the extent of their support, revealing itself in ways I never thought possible even just a couple of years ago. I am eternally thankful for their sage advice, and that's why this thesis is dedicated to them. Although I may not be visibly demonstrative of my appreciation all the time, I hope that they can recognize how much their support has meant to me.

Hmm. Even my acknowledgments section is too long.

ABSTRACT

Oxidation is a fundamental process in chemistry and biology. In synthetic chemistry, several developments have been made in catalytic asymmetric oxidative transformations that involve a heteroatom transfer from a reagent to a substrate (e.g., epoxidations, dihydroxylations). Enantioselective oxidations that do not involve a heteroatom transfer have been relatively less explored. These types of oxidative transformations were investigated using a general palladium(II) catalyst system.

A palladium-catalyzed oxidative kinetic resolution of secondary alcohols was developed. This catalytic system utilizes (–)-sparteine as the chiral ligand and molecular oxygen as the sole stoichiometric oxidant. Benzylic and allylic alcohols can be resolved to high enantiomeric excesses in excellent yields. The same selective process has been applied to the desymmetrization of meso diols.

This general palladium(II) oxidative system was applied to intramolecular Wacker oxidations to form a variety of heterocycles. Lactones, lactams, tetrahydrofurans, dihydrobenzofurans, and dihydrobenzopyrans were all accessed by this methodology. Importantly, this work provided entry into the development of asymmetric variants. Highly enantioselective cyclizations of phenolic substrates were realized with a palladium-sparteine catalyst, analogous to the kinetic resolution chemistry. The heterocyclization chemistry was employed in the context of the total synthesis of the *Cephalotxaxus* alkaloids.

Oxidative annulations for the synthesis of carbocycles were developed utilizing this general palladium system. Indoles with pendant olefin tethers were oxidatively

cyclized under palladium(II) catalysis to form annulated indoles. Electron-rich aromatic systems were also investigated, culminating in the syntheses of benzofurans and dihydrobenzofurans. These reactions were demonstrated to proceed by an initial C-H bond functionalization event, followed by olefin insertion and β-hydride elimination.

Enantioselective heterocyclizations using the general oxidative system were further explored. Promising results were realized in the heterocyclizations of sulfonamide-based compounds. Key experiments allowed for a firmer understanding of how the reaction was progressing and, specifically, how enantioselectivity was being induced by the palladium catalyst.

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LIST OF ABBREVIATIONS

$[\alpha]_D$	specific rotation at wavelength of sodium D line
Ac	acetyl
AIBN	2,2'-azobisisobutyronitrile
t-Am	*tert*-amyl
app.	apparent
aq.	aqueous
Ar	aryl
atm	atmosphere
BBN	borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
BOM	benzyloxymethyl
bp	boiling point
br	broad, broadened
Bu	butyl
i-Bu	isobutyl
n-Bu	*n*-butyl
t-Bu	*tert*-butyl
Bz	benzoyl
c	concentration for specific rotation measurements
° C	degrees Celsius
calc'd	calculated
cat.	catalytic
comp	complex
conv	conversion
Cy	cyclohexyl
d	doublet
dba	dibenzylideneacetone

DCC	dicyclohexylcarbodiimide
DCE	1,2-dichloroethane
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminum hydride
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMFDMA	*N,N*-dimethylformamide dimethyl acetal
DMSO	dimethylsulfoxide
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dr	diastereomeric ration
ee	enantiomeric excess
EI	electrospray ionization
equiv	equivalents
er	enantiomeric ratio
Et	ethyl
FAB	fast atom bombardment
g	grams
GC	gas chromatography
[H]	reduction
h	hours
HMDS	hexamethyldisilazane or hexamethyldisilazide
hν	light
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
imid.	imidazole
IR	infrared
J	coupling constant
kcal	kilocalories
L	liter

LAH	lithium aluminum hydride
LDA	lithium dicyclohexylamide
M	metal or molar
m	milli or multiplet or meters
m/z	mass to charge ratio
μ	micro
Me	methyl
Mes	mesityl
MHz	megahertz
min	minutes
mol	moles
mp	melting point
MS	molecular sieves
Ms	methanesulfonyl
N	normal
ν	frequency
nbd	norbornadiene
NBS	*N*-bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
[O]	oxidation
o	ortho
OKR	oxidative kinetic resolution
p	para
PCC	pyridinium chlorochromate
n-Pent	*n*-pentyl
Ph	phenyl
pH	hydrogen ion concentration in aqueous solution
PhH	benzene
Piv	pivaloyl (trimethylacetyl)

pK_a	acidity constant
PPA	polyphosphoric acid
ppm	parts per million
PPTs	pyridinium *p*-toluenesulfonate
i-Pr	isopropyl
py	pyridine
pyr	pyridine
q	quartet
ref	reference
R_F	retention factor
s	singlet or selectivity factor
sat.	saturated
SEM	(trimethylsilyl)ethoxymethyl
stoich.	stoichiometric
Sub	substrate
t	triplet
TBAF	tetrabutylammonium fluoride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy, free radical
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid or trifluoroacetate
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin-layer chromatography
TMG	1,1,3,3-tetramethylguanidine
TMS	trimethylsilyl
TOF	turnover frequency
TON	turnover number
TPAP	tetrapropylammonium perruthenate

Ts	*p*-toluenesulfonyl or tosyl
TsOH	*p*-toluenesulfonic acid or tosic acid
UV	ultraviolet
v/v	volume to volume
w/v	weight to volume