Application of Transition Metal Catalysis to Small Molecule Synthesis

Thesis by

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In Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy

California Institute of Technology

Pasadena, California

2006

(Defended July 29, 2005)

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Acknowledgement.

It is absolutely amazing that five years have passed since I came to Caltech. It is even more amazing that this thesis is now in its final hours. I can honestly say that these five years have been the absolute best of my life thus far. The environment for learning here is amazing, primarily because of the large number of talented people that fill it, from whom I have gotten countless ideas, advice, and inspiration.

First and foremost, of course, I acknowledge Bob Grubbs, my advisor. Deciding to work for him was the best move that I could have made. I really appreciate the freedom that Bob allowed me, both with respect to the hours that I worked and the nature of the research that I carried out. I have become a very independent and self-motivated worker, thanks to the environment that Bob has created in his research group. Bob also provided me with the direction that I needed. Essentially all of my publications have come from projects that he suggested to me. His hand was critical in keeping me moving ahead in my research, as I have the natural tendency to study a system until it has been driven ten feet under the ground. Another wonderful aspect of working in the Grubbs group has been our annual camping trip, which I thank Bob for providing. Finally, Bob is just a really nice guy, which has also made these five years very pleasant ones.

Next I want to thank my committee members: Dave MacMillan, Brian Stoltz, Jonas Peters, and Jackie Barton. Both my candidacy exam and my propositions exam were positive and beneficial experiences. In addition to serving on my committee, Brian and Dave both agreed to write letters of recommendation for me when I was applying for jobs, and both of them (indirectly, via conversations with Bob) have given me very helpful suggestions regarding my research. I especially want to thank Brian for agreeing

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to jump onto my committee at the end, when schedule conflicts arose with another member, even though I am certain that he was already on a million other committees. Brian also taught an excellent organic synthesis class.

Next on my list is J. P. Morgan. J. P. was a graduate student when I first joined the Grubbs group. He took me under his wing and let me work on his project. I arrived having never even run a column, and J. P. taught me almost everything that I know about doing organic synthesis. I spent a lot of time talking to him during my first couple of years at Caltech. He had a lot of good advice, and he was extremely patient with me, always explaining everything carefully and thoroughly.

I want to thank Dan Sanders, another past graduate student, as well. I shared a bay with Dan for 4 years. He was a lot of fun to work with, and we spent many a late night in the lab together. Dan also gave me a lot of good advice, especially when I was preparing for the interview process, and he provided empathy as I agonized over the woes of doing chemistry.

I want to thank Chris Douglas, a postdoc who joined our group less than a year ago. Chris ended up working on my bench with me when he arrived, since all spaces were filled to capacity and I was about to start writing. He was a really fun person to work with, and I greatly appreciate his patience with respect to having to work around all of my junk.

I thank all of the numerous past group members, who gave me an abundance of helpful advice, or who were just fun people to talk to. Specifically, I want to mention Steve Goldberg, Jen Love, Brian Connell, and Justin Gallavan. I also want to acknowledge Dean Toste and Arnab Chatterjee, who provided the groundwork for some

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of the projects that I worked on here. Paula Diaconescu helped me use the glove box during my last project. Oren Scherman kept me company during the ACS meeting in New York, and Andrew Waltmann was the only person who would go hiking with me during our first camping trip (though our group has gained a lot of hikers since then). Many others have also provided me with good memories, which there is not space to mention.

I also want to thank the current members of the Grubbs group, who have contributed greatly to my graduate school experience. Jason Jordan, Tim Funk, Jacob Berlin, and Andy Hejl have all been here almost as long as I have. They are a really good group of guys. I will remember Jason for our discussions about Harry Potter; Tim for our collaboration on part of one of my projects, as well as many interesting discussions; Jacob for being a very ambitious hiker; and Andy for mistaking me for a bear during our last camping trip in Sequoia. I also want to thank Erin Guidry and Donde Anderson. Several years ago they saved me from becoming the only female in the group, and they have always been a lot of fun to talk to. They also resurrected girls' lunch, which has been great ever since. Anna Wenzel has provided helpful proofreading for me, and I've enjoyed watching classic movies at her house, while her crazy bird danced in its cage. I want to thank everyone else in the Grubbs group as well, because they have all made the environment here a good one.

I want to thank everyone in the Stoltz and the MacMillan groups. These people have always been willing both to let me use their instruments and to take the time to teach me how to use them. I especially thank Neil Garg, Doug Behenna, and Dan Caspi for help with the NMR and the HPLC.

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I want to acknowledge the entire staff in the Caltech Chemistry Department. They are all wonderful people, and they keep this place running. I especially thank Linda Syme, Bob's secretary; Dian Buchness, the department secretary; Chris Smith, who coordinated all of the on-campus job interviews; and Rick Gephardt, the glass blower. A special thanks also goes to Tom Dunn and Silva Stepanian for saving my data and putting my computer back together when its hard drive gave out right in the middle of the thesiswriting process. They were lifesavers.

I want to thank the good friends that I have made while living in Pasadena, as they have all helped me in many ways. Amanda Cashin, Xin Qui, and Jessica Mao, fellow students from my class, have been good friends throughout my time here. Crystal, Dave, and Jason Vaughan, who have nothing to do with Caltech or even science, were really good friends as well, especially during my earlier years here. They provided a sense of balance in my life, and Jason learned to swing dance with me. Lyle Chamberlain, a Caltech undergrad, became a good friend during the latter half of my time in graduate school. In my circle, undergrads were generally viewed as being somewhat odd, but Lyle showed me otherwise, and he taught me a lot about robots too.

I want to thank my family. They, of course, provide the basis upon which I do everything else. I am so glad that I have them, and I am grateful that all of us are friends. My father, a chemist, was a big part of the reason for my decision to pursue chemistry. He has provided me with a summer internship (many years ago), a lot of good advice, and even proofreading services.

Finally, I want to acknowledge Greg Beutner. His arrival in our group last summer could not have been timelier. Greg was immediately excited about my research

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and provided me with countless advice and new ideas. He is one of the smartest, most creative, and enthusiastic chemists that I have ever met. His attitude was contagious, and it helped me to become more excited about my project. Greg became my number one person to talk to about things, in part because he was so helpful, and in part because I had a crush on him. Those were very fun days, and, so far, they have ended well, because Greg eventually asked me out, and things have been spectacular ever since. During my thesis-writing process, Greg has provided a lot of support, including proofreading my entire thesis, making me dinner *every* night, and being patient when I freaked out because I thought it was never going to be done, which happened on a regular basis. Greg has been a wonderful addition to my life.

Abstract

Over the past decade, transition metal catalysis has developed into a new field in organic synthesis, enabling numerous synthetic transformations that were previously not feasible. This thesis describes the application of both ruthenium and rhenium catalysis to the synthesis of several classes of small molecules. Ruthenium-catalyzed ring-opening cross-metathesis of five- through eight-membered ring cycloolefins was investigated for the synthesis of functionalized dienes (Chapter 1). Unsubstituted, trisubstituted, and allyl-substituted cycloolefins were studied. Regioselective reactions could be achieved with the use of unsymmetrical cycloolefins. Ruthenium-catalyzed cross-metathesis was explored for the synthesis of both di- and trisubstituted vinyl boronates (Chapter 2). These reactions proceeded efficiently for a wide variety of functionalized alkenes and generally exhibited high *E*-stereoselectivity. The resultant vinyl boronate products were stereoselectively converted into both Z-vinyl bromides and E-vinyl iodides. The rhenium-catalyzed 1,3-isomerization of allylic alcohols was employed in the synthesis of various allylic alcohols (Chapter 3). Two different strategies were developed to promote high product selectivity in these reactions: conjugated product synthesis and N,Obis(trimethylsilyl)acetamide-promoted product trapping. These reactions enabled the synthesis of allylic alcohols with conjugated or non-conjugated, di- or trisubstituted, and electron-rich or electron-deficient alkene components. Partial chirality transfer was observed during the 1,3-isomerization of certain enantioenriched allylic alcohols. The fundamental reaction properties observed during these studies were all consistent with the operation of a mechanism involving a chair-like transition state, which contains a partially cationic allyl moiety, as the primary reaction pathway.

General Experimental Section

NMR spectra were recorded on an Oxford NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to the internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad (br). The reported ¹H NMR and ¹³C NMR data refer to the major alkene isomer (which is identified) except when otherwise noted. Assignment of the E/Z stereochemistry for the disubstituted alkenes was based upon the coupling constants of their vinylic protons, and that for the trisubstituted alkenes was based upon NOE experiments. High-resolution mass spectra (EI, CI, or FAB) were provided by the California Institute of Technology Mass Spectrometry Facility. Molecular mass calculations were performed with ChemDraw Ultra 9.0.1 (Cambridge Scientific).

GC and HPLC data were obtained using an Agilent 6850 Series GC system and an Agilent 1100 Series HPLC, respectively. Optical rotations were measured using a Jasco P-1010 Polarimeter. Low reaction temperatures (-10 °C to -50 °C) were obtained using a Neslab CC-100 Cryotrol. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed using a standard potassium permanganate stain. Flash column chromatography employed silica gel 60 (230-400 mesh) from EM Science. Ether, CH₂Cl₂, benzene, and THF were purified and dried by passage through a solvent column.ⁱ All other chemicals were used as purchased, unless otherwise noted.

¹ The solvent columns were composed of activated alumina (A-2) and supported copper redox catalyst (Q-5 reactant). See: Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

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