Chemo- and Stereoselective Olefin Metathesis in Small Molecule Synthesis

Thesis by

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I worked on a few projects with other group members. Dr. Christie Morrill let me work on vinyl boronate cross-metathesis with her after my stint in catalyst design ended, and Dr. Jon Efskind and I spent some time working on conjugated diene cross-metathesis. They were both good experiences and great people to work with. Christie was always up for a good conversation about religion, and Jon let me use the swimming pool in his apartment complex. For the last few years I worked with Jacob Berlin on enantioselective olefin metathesis. I argued a lot more with Jacob than I did with any of the other people I worked with, but it was always for the good of the chemistry. And because we both like to argue. He's got a unique view of chemistry, and I learned a lot from him. He was also my injury-prone softball coach and surfing buddy.

Four of us joined the Grubbs group from the incoming graduate class of 2001: Andy Hejl, Jason Jordan, Jacob Berlin, and I. Andy and I have been friends since before we joined the group thanks to our shared interest in becoming independently wealthy. Over the years we've talked about chemistry, hosted 4 Thanksgiving Extravaganzas, brewed beer, played golf, and traveled to Hawaii. Jason and I worked beside each other in the lab for a couple of years, and he was always an interesting guy to talk to. He, Andy, and I also drove to most of the camping trips together, and now we share a common interest in fine music.

There are too many other group members to thank individually, so I'll thank all of them at once. Everyone had a different background and different interests, which is one of the things that makes the Grubbs group unique. People ask questions about things other people never considered, and attempts to solve problems in one field led to solutions in another. I learned a lot from everyone, and I greatly appreciate it. They were all fun people to hang out with, too, and they made the camping trips and pub crawls memorable.

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Abstract

The development of well-defined ruthenium alkylidenes has played a large role in turning olefin metathesis into a transformation that is widely used in many fields of synthetic chemistry. The success of ruthenium catalysts can be attributed to their high activity in combination with their air and moisture stability and functional-group tolerance. Unlike many early transition metal alkylidene complexes, ruthenium catalysts react with alkenes selectively over many common functional groups. Along those lines, the major goals of the work described in this dissertation were to expand the selectivity of ruthenium metathesis catalysts to include chemo- and stereoselective reactions and to apply those reactions to the synthesis of important organic compounds.

Chapter 2 describes efforts to synthesize trisubstituted vinyl boronates using the cross-metathesis of 1,1-disubstituted vinyl pinacol boronates. The reactions with methyl-substituted substrates afforded products in modest yields (up to 60%), and the reactions were typically highly selective for the *Z*-alkene. As the size of the substituent increased, the yields and stereoselectivities decreased. The lack of reactivity of certain ruthenium catalysts in the formation of trisubstituted alkenes lent insight into how to develop a chemoselective reaction where a monosubstituted olefin would exclusively react in the presence of a more highly substituted olefin.

Chapter 3 describes how conjugated dienes were synthesized by taking advantage of the large reactivity difference between a monosubstituted alkene and a 1,1-disubstituted alkene. The cross-metathesis reactions were highly chemo- and stereoselective, and only the *E*-isomer of the products was formed. Additionally, further

functionalization of the diene products was shown to be possible in a one pot cross-metathesis/Suzuki coupling process.

The research presented in chapters 4 and 5 focused on the asymmetric ring-closing metathesis of achiral trienes using chiral ruthenium catalysts. Chapter 4 describes how substitution on the chiral catalyst and the substrate affected the enantioselectivities of the ring-closing reactions. It was discovered that certain five-, six-, and seven-membered rings could be made in ≥90% *ee* with the chiral ruthenium catalysts. The application of asymmetric ring-closing metathesis in the synthesis of (+)-5-*epi*-citreoviral is presented in chapter 5. The absolute configuration of one chiral center was set using asymmetric ring-closing metathesis, and the remaining three stereocenters were generated from that chiral center.

In addition, there are two appendices. Appendix 1 contains comments on the formation of tetrasubstituted olefins using unhindered ruthenium catalysts. The results from research directed towards the generation of a cis-selective olefin metathesis catalyst bearing a bidentate ligand are described in appendix 2.

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