Chemo- and Stereoselective Olefin Metathesis in Small Molecule Synthesis

Thesis by

Timothy William Funk

In Partial Fulfillment of the Requirements

for the Degree of

Doctor of Philosophy

California Institute of Technology

Pasadena, California

2007

(Defended June 12, 2006)

Acknowledgements

First and foremost, I want to thank Prof. Bob Grubbs. He allowed me to explore my own interests and take projects in the directions that I wanted to take them. His vast knowledge and practical approach to problem solving were invaluable. For every bit of chemistry he passed on, there was always a story about the people who did the work to go along with it. Additionally, he took me rock climbing, let me swim in his pool, let the whole group go camping for 5 days a year, and did not make fun of me when I grew a "beard." I appreciate all of it.

One of the best parts about being a graduate student at Caltech was the constant exposure to very intelligent people. The first group I'd like to thank is my thesis committee (Prof. Dennis Dougherty, Prof. Brian Stoltz, Prof. Jonas Peters, and Prof. John Bercaw). I took, or at least audited, classes from all of my committee members, and they are all great teachers that continued to educate me outside of the classroom.

The next group I'd like to thank is the Grubbs group. I joined in December of 2001 and started working on a project in January of 2002. Although I was the only one actively working on the project, I got a lot of help from Dr. Steve Goldberg, Prof. Jen Love, Prof. J. P. Morgan, and Dr. Tina Trnka. Steve helped me with the organic chemistry, Jen with the glovebox, J.P. with all general metathesis questions, and Tina with inorganic and organometallic chemistry. I appreciate all your help and patience.

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.

One other group stands out as playing an important role in my education over the years; the Friday afternoon journal club crew. The people that attended those informal meetings, consisting mainly of Stoltz group members, taught me a lot of chemistry during those metal clubs, synthesis clubs, and mechanism clubs. Thanks.

The staff at Caltech is great and makes things run smoothly. Dian, Linda, and Anne always had the answers to my nonchemistry questions. Between Chem 5a students and me breaking glassware, I spent a lot of time talking to Rick about what he could fix (actually, what can't he fix?) and about what cool tropical paradise I should travel to. Although he doesn't work for Caltech, I certainly need to thank Dan Nieman for all his help with the solvent columns and for his stories about LA in the 1950s.

Although I'm not sure who to thank for this, I appreciate the fact that I remained sane in graduate school because I had a life outside of the lab. All of the intramural sports teams (especially Imperial Palace) kept me exercising and meeting new people. I looked forward to weekly trips to the beach to go surfing and to Fridays at the Ath. And I always looked forward to coming home to my wife, Amy, who was incredibly supportive of me during my time at Caltech.

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.

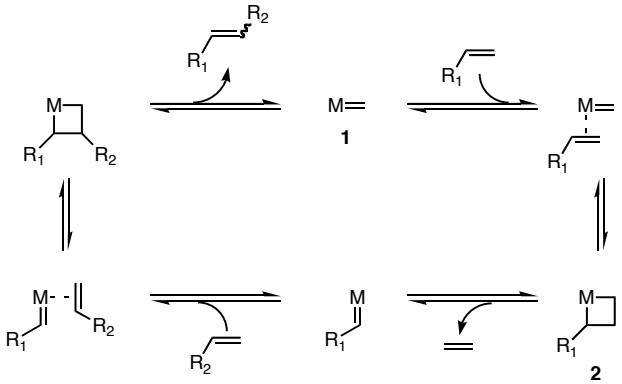
The research presented in chapters 4 and 5 focused on the asymmetric ring-closing metathesis of achiral trienes using chiral ruthenium catalysts. Chapter 4 describes how substitution on the chiral catalyst and the substrate affected the enantioselectivities of the ring-closing reactions. It was discovered 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.

Table of Contents

Chapter 1
Introduction

The olefin metathesis reaction is a powerful synthetic tool that scrambles the carbon atoms of carbon–carbon double bonds and creates new carbon–carbon double bonds. The mechanism of the reaction was proposed by Chauvin in 1971, and it is still accepted today (Scheme 1.1).[1] The key component to any olefin metathesis reaction is a transition metal species bearing a metal–carbon double bond (carbene or alkylidene). An alkene approaches the alkylidene (**1**) and undergoes a [2+2]-cycloaddition that generates a new carbon–carbon bond and affords a metallocyclobutane (**2**). A retro-[2+2], where different bonds break than were formed, generates a new olefin and a new metal alkylidene.



Scheme 1.1. Accepted olefin metathesis mechanism.

This simple transformation has been used in a wide variety of ways to synthesize simple organic molecules, complex natural products, supramolecules, and polymers.[2] Some of the common reactions are shown in Figure 1.1. Cross-metathesis (CM), ring-opening/cross metathesis (ROCM), and ring-closing metathesis are used in small molecule synthesis, and acyclic diene metathesis polymerization (ADMET) and ring-

opening metathesis polymerization (ROMP) are processes that generate oligomers and polymers. These reactions are reversible, and in many cases the driving force for product formation is the release of gaseous by-products such as ethylene or the release of ring strain.

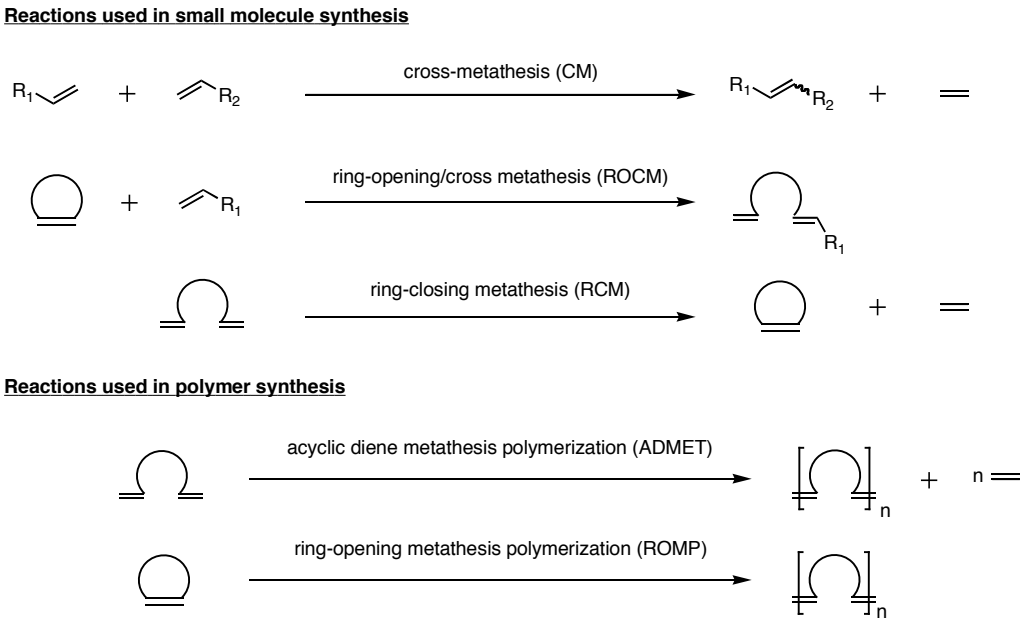
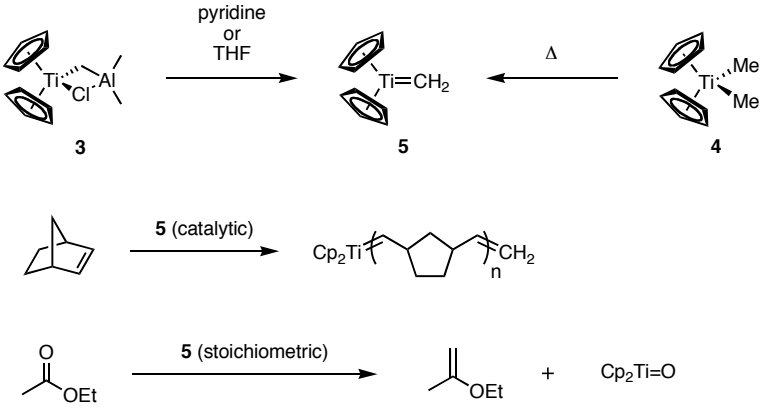


Figure 1.1. Common olefin metathesis reactions.

Although the olefin metathesis reaction has been known since the 1960s,[3] it was not until the development of well-defined, homogeneous catalysts that it found applications in organic synthesis. There are many transition metal alkylidenes that catalyze olefin metathesis reactions to some degree, but complexes based on titanium, molybdenum, and ruthenium receive the most use.[4] The different metals impart different reactivities to the alkylidenes, and, even within a family of complexes derived from one metal, small adjustments in the ligand environment cause large changes in catalyst behavior. Generally, early transition metal alkylidenes are more oxophilic than late metals complexes, and this property has a large impact on the chemoselectivity of the catalyst.

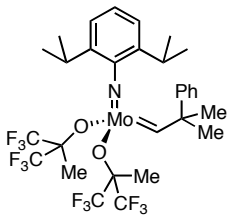
The most commonly used titanium alkylidenes are generated in situ from either Tebbe's reagent (**3**)[5] or dimethyltitanocene (**4**)[6] (Scheme 1.2). These compounds form a titanium methylidene, which can catalyze the ROMP of strained olefins. Other alkenes can react with titanium methylidenes to afford titanacyclobutanes, but an efficient catalytic cycle does not typically occur. The low reactivity of titanium alkylidenes allowed them to act as model systems and provide valuable insight into the olefin metathesis reaction.[7] Due to their high oxophilicity and the stability of the Ti–O bond, these complexes will react stoichiometrically with aldehydes, ketones, esters, lactones, and amides to afford methylenated products.[8] Although these complexes are not typically used as olefin metathesis catalysts, they have found a place in organic synthesis as carbonyl methylenating agents.



Scheme 1.2. Reactions of titanium methylidenes.

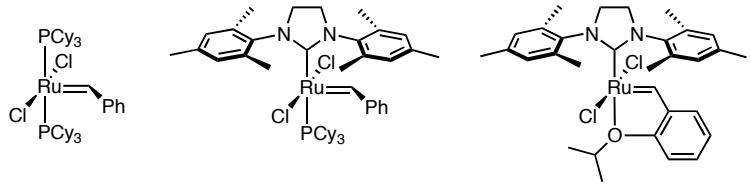
Many different molybdenum and tungsten alkylidenes have been synthesized,[9] and the catalyst that is used most often is **6**.[10] It is much more active that the titanium catalysts in performing olefin metathesis, and it has been applied to organic and polymer synthesis. The main disadvantage of the molybdenum-based catalysts is their air and moisture sensitivity as well as their reactivity with oxygen-containing functional groups.

Carboxylic acids, primary amines, aldehydes, most alcohols, and some ketones react with them and remove them from the olefin metathesis catalytic cycle. These functional groups are found in many organic compounds, limiting the use of the molybdenum catalysts.



6

The main disadvantage of the early transition metal catalysts presented above is a lack of selectivity for olefins over other functional groups, and selectivity is a crucial part of any synthetic methodology. Some of the most successful reactions used in organic chemistry are those that reliably react with a certain functional group in a certain way and do not disturb the rest of the molecule. It was the development of ruthenium olefin metathesis catalysts that bridged the gap between olefin metathesis and organic synthesis.[11] Due to the functional group tolerance of ruthenium catalysts, olefin metathesis has become a selective reaction that has found widespread use among organic and polymer chemists. Just as in the case of molybdenum, many different metathesis-active ruthenium catalysts are known. A few of the most common catalysts are shown in Figure 1.2.[12] All three alkylidenes are stable to air and moisture, and complexes **8**[12b] and **9**[12c] exhibit catalytic activities similar to those of the highly active molybdenum systems.



7 **8** **9**

Figure 1.2. Selected ruthenium olefin metathesis catalysts.

This brief introduction has not done justice to all of the time and effort that has been dedicated to understanding olefin metathesis and developing it into a reliable, practical reaction. However, it has illustrated the importance of selectivity. Unlike the early transition metal-based alkylidenes, the ruthenium catalysts react preferentially with alkenes over many common functional groups, so they are the catalysts of choice in synthetic organic chemistry. But another question remains: could these ruthenium catalysts (or derivatives thereof) react selectively with one alkene in the presence of more than one? The exploration of chemo- and stereoselective olefin metathesis and its application in the synthesis of important organic compounds is presented in the following chapters of this dissertation.

As described in chapter 2, the synthesis of trisubstituted vinyl boronates using catalyst **8** was moderately successful. The lack of reactivity of catalyst **8** toward 1,1-disubstituted alkenes discovered during the work in chapter 2 afforded insight into how to develop a chemoselective olefin metathesis reaction. The research presented in chapter 3 focuses on the chemoselective CM of substituted conjugated dienes. This reaction generates compounds that are known to be versatile synthetic intermediates and are found in natural products. Chapter 4 contains the results from a study on asymmetric ring-closing metathesis (ARCM) that used chiral derivatives of **8**. All of the substrates were achiral trienes, and the extent to which a catalyst reacted with one alkene over another

was determined by the enantiomeric excess of the chiral products. The application of ARCM in the enantioselective total synthesis of (+)-5-*epi*-citreoviral is presented in chapter 5. Finally, comments on the formation of tetrasubstituted olefins using unhindered ruthenium catalysts are presented in appendix 1, and the results from research directed toward the generation of a cis-selective olefin metathesis catalyst bearing a bidentate ligand are described in appendix 2.

References

[1] Hérrison, J.-L.; Chauvin, Y. *Makromol. Chem.* **1971**, *141*, 161–167.

[2] For a comprehensive review of applications in organic and polymer synthesis, see *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2 and Vol. 3.

[3] (a) Truett, W. L.; Johnson, D. R.; Robinson, I. M.; Montague, B. A. *J. Am. Chem. Soc.* **1960**, *82*, 2337–2340. (b) Natta, G.; Dall'Asta, G.; Mazzanti, G.; Passquon, J. *J. Polymer Sci., Polymer Lett.* **1964**, *B2*, 349.

[4] For a review on the history of metathesis catalyst development, see *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1.

[5] (a) Tebbe, R. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611–3613. (b) Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W. *J. Am. Chem. Soc.* **1979**, *101*, 5074–5075.

[6] Claus, K.; Bestian, H. *Justus Liebigs Ann. Chem.* **1962**, *654*, 8.

[7] Grubbs, R. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, Chapter 1.2.

[8] Petasis, N. A.; Bzowej, E. I. *J. Am. Chem. Soc.* **1990**, *112*, 6392–6394.

[9] For reviews on molybdenum and tungsten olefin metathesis catalysts, see (a) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633. (b) Schrock, R. R In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, Chapter 1.3.

[10] Schrock, R. R.; Murdzek, J. S.; Bazan, G. C.; Robbins, J.; DiMare, M.; O'Regan, M. *J. Am. Chem. Soc.* **1990**, *112*, 3875–3886.

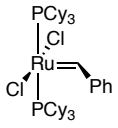
[11] Nguyen, S. T.; Trnka, T. M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 1, Chapter 1.6.

[12] (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W.; *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (c) Carber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168–8179.

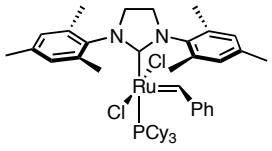
Chapter 2
Ruthenium-Catalyzed Olefin Cross-Metathesis of α-Substituted Vinyl Boronates

Introduction

The development of active, air- and moisture-stable ruthenium alkylidene catalysts (i.e., **1** and **2**) has allowed olefin metathesis to become a powerful tool in synthetic chemistry.[1] As discussed in the previous chapter, a variety of intramolecular and intermolecular reactions involving olefin metathesis can be applied to small molecule and polymer synthesis. This chapter will focus only on cross-metathesis (CM) and how substrate substitution affects the distribution of products. More specifically, the application and limitations of catalyst **2** in the synthesis of trisubstituted vinyl boronates will be discussed.



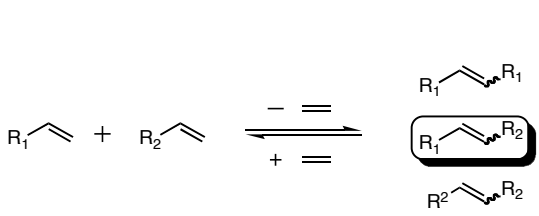
1



2

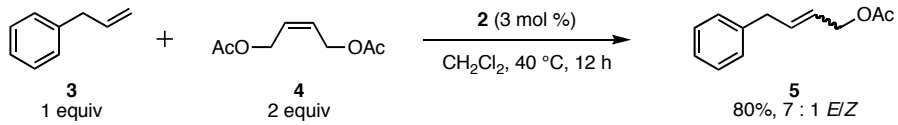
Olefin CM, at first glance, appears to be a simple approach to coupling two alkenes. Unfortunately, because the reactive functionalities are the same (two carbon–carbon double bonds), a mixture of homocoupled and heterocoupled products can be formed (Scheme 2.1).[2] This type of complication is not present when other transition metal-catalyzed reactions (i.e., coupling of an aryl halide with an arylboronic acid) are used. When a highly active complex such as **2** catalyzes the CM reaction of simple terminal alkenes, a statistical distribution of products is obtained.[3] The catalyst does not differentiate between the two olefins, and secondary metathesis continues to shuffle the

products until equilibrium is reached. Almost 10 equivalents of one olefin must be used to obtain heterocoupled product in 90% yield. One example that illustrates the lack of selectivity of CM is shown in Scheme 2.2. One equivalent of allyl benzene (**3**) reacts with two equivalents of *cis*-1,4-diacetoxy-2-butene (**4**) (equal to four equivalents of allyl acetate) to give the heterocoupled product in an 80% yield.[3a] Additionally, a mixture of olefin isomers is obtained.



$R_1 : R_2$	CM product selectivity
1 : 1	50%
2 : 1	66%
4 : 1	80%
10 : 1	91%
20 : 1	95%

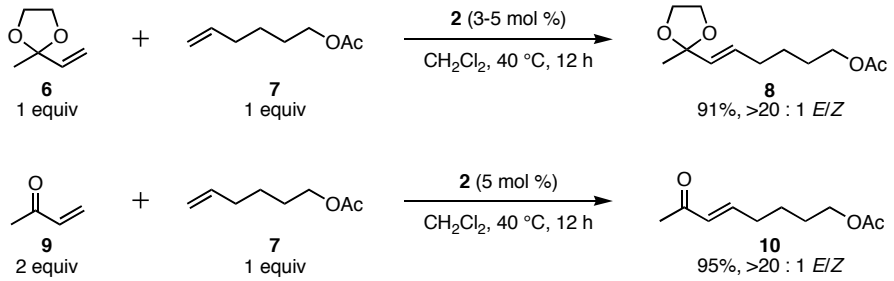
Scheme 2.1. Statistical distribution of products obtained during CM.



3 1 equiv **4** 2 equiv **5** 80%, 7 : 1 *E*/*Z*

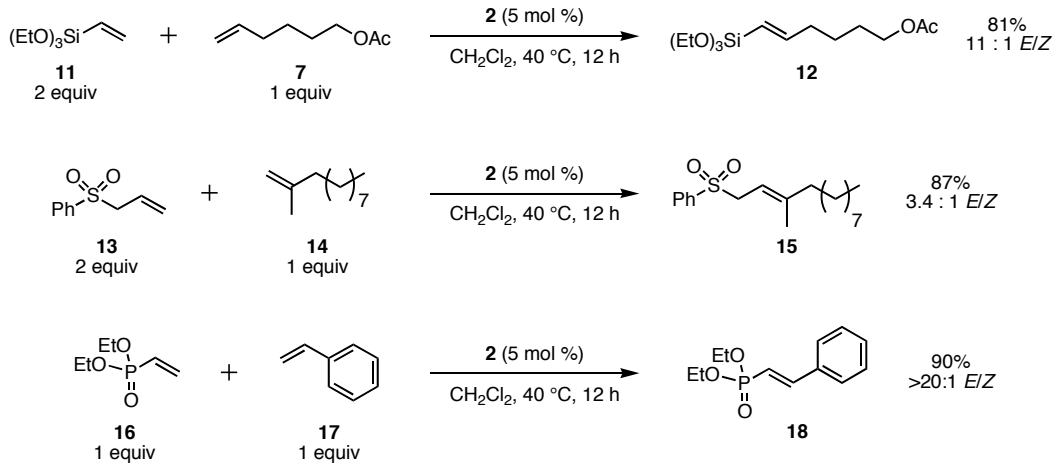
Scheme 2.2. CM of allyl benzene (**3**) and *cis*-1,4-diacetoxy-2-butene (**4**).

It was discovered that one way to promote selective CM is to introduce substitution close to the reacting alkene.[3,4] As illustrated in Scheme 2.3, bulky allylic substitution and electron-withdrawing groups in conjugation with the olefin result in a CM reaction selective for the heterocoupled product and the *E*-isomer.[3a,5] These olefins undergo homocoupling either very slowly or not at all, so the CM equilibrium is shifted toward the heterocoupled products. The relative reactivities of olefins in CM is catalyst dependent: catalysts **1** and **2** homocouple the same olefins with different efficiencies.[3] Therefore, by choosing the appropriate catalyst for a given CM reaction, high selectivity for the desired product can be achieved.



Scheme 2.3. Selective CM using one alkene that does not readily homocouple.

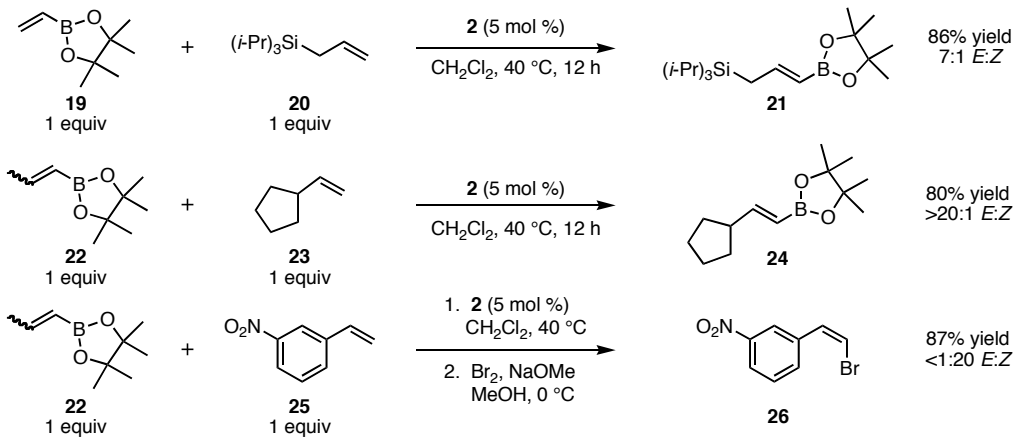
In order for CM to be a practical synthetic tool, functionalized intermediates that can undergo further manipulation must be accessible. Ruthenium benzylidene **2**, due to its high activity and tolerance of a wide variety of functionality, can catalyze the CM of olefins with allylic and vinylic substitution (Scheme 2.4).[3,6] Additionally, because the functionalized olefins typically do not homocouple readily, the reactions are selective for the heterocoupled products. The CM products can be further functionalized, sometimes even without isolation.[7]



Scheme 2.4. CM with allyl and vinyl functionalized olefins.

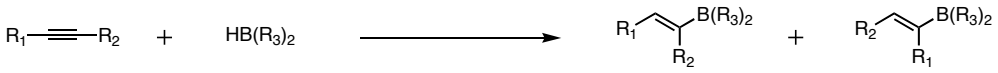
One type of functionality that is tolerated by catalyst **2** is vinyl pinacol boronates.[8] Vinyl boronates can be converted into aldehydes or ketones,[9] halides,[10] amines,[9b] and carbon containing groups[11] and are therefore valuable synthetic intermediates. Christie Morrill, a former graduate student in the group, showed that vinyl pinacol boronate (**19**)

and 1-propenyl pinacol boronate (**22**) could undergo CM selectively with many different alkenes to form 1,2-disubstituted vinyl boronates (Scheme 2.5).[8] Additionally, she illustrated that the vinyl boronate cross products could be converted to vinyl bromides in situ (two-step formation of **26**).



Scheme 2.5. CM with vinyl pinacol boronates and further functionalization.

1,2-Disubstituted vinyl boronates are typically made by the hydroboration of a terminal alkyne, which generally occurs with high regioselectivity.[9a,12] On the other hand, trisubstituted alkenes, which are made by the hydroboration of an internal alkyne, are often obtained as a mixture of isomers due to low regioselectivities (Scheme 2.6).[13] Cross-metathesis does not suffer from the same regiochemical issues that can plague hydroboration, so the synthesis of trisubstituted vinyl boronates from α-substituted vinyl pinacol boronates was explored.[14]



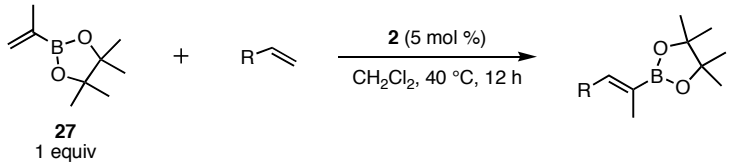
Scheme 2.6. Regioselectivity issues in the hydroboration of internal alkynes.

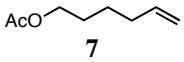
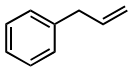
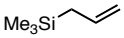
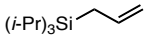
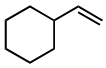
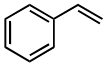
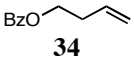
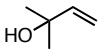
Results and Discussion

The first α-substituted vinyl pinacol boronate that was used was 2-propenyl pinacol boronate (**27**). This compound was readily synthesized from trimethyl borate, 2-propenyl magnesium chloride, and pinacol,[8] and it was stable to flash chromatography. The first reaction that was examined was the CM between **27** and 5-hexenyl acetate (**7**) (Table 2.1, entry 1), because the products were stable and separable from the starting materials by flash chromatography. The highest yield was observed when 2 equivalents of **27** were used: attempts to increase the yield using longer reaction times and higher temperatures were unsuccessful. Only the *Z*-isomer (carbon takes precedence over boron in the naming of *E* and *Z* isomers) was obtained. Unreacted vinyl boronate was always present in the reaction mixture, even after 24 h.

Cross-metathesis reactions of **27** with other olefins were explored, and, generally, the products were obtained in moderate yields, with the highest yield being 60% (Table 2.1). The *Z*:*E* selectivity was high in most reactions; the low diastereoselectivity in entry 9 may have been due to coordination of the benzoyl group to the catalyst.[15] The only trisubstituted vinyl boronates that were cleanly isolated from unreacted **27** were those obtained from reactions with **7**, **34**, and **35**; in all cases unreacted **27** remained. When polar functional groups were introduced to the allylic and homoallylic positions of the cross partners, low yields (<50%) were obtained.

Table 2.1. CM reactions of 2-propenyl pinacol boronate (**27**).



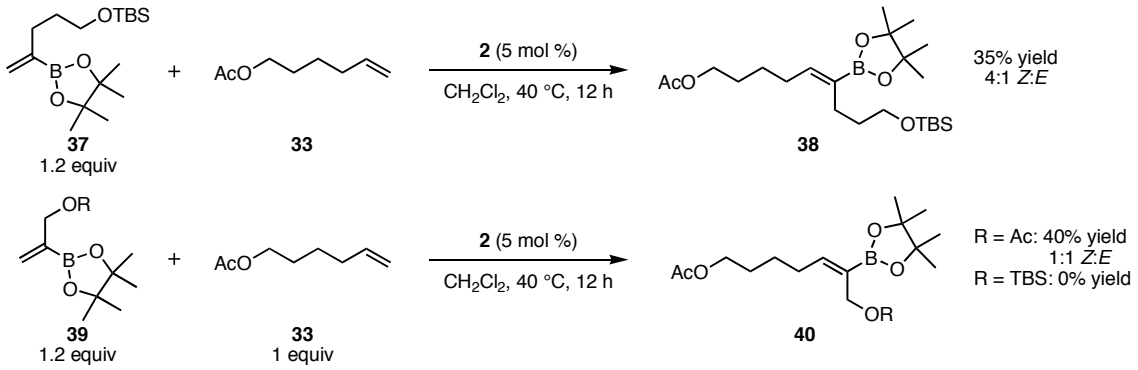
Entry	Cross Partner	Equiv	Product/1	Yield (%)[a]	*Z*:*E*
1	 **7**	0.5	–	58	>20:1
2	 **28**	2	5.5:1	59	7:1
3	 **29**	1	3.4:1	59	>20:1
4	 **30**	1	5:1	60	>20:1
5	 **31**	1	3.3:1	44	>20:1
6	 **32**	1	1:3	14	>20:1
7	 **33**	2	1.4:1	34	>20:1
8	 **34**	1	–	46	>20:1
9	 **35**	0.5	–	30	2:1
10	 **36**	1	–	0	–

[a] Yields for all entries except 1, 8, and 9 determined by ^{1}H NMR spectroscopy.

Compared to CM reactions with **19** and **22**,[8] most products were formed in much lower yield with **27**. For example, **22** reacted with 1 equiv of **30** to afford the cross product in 99% yield, which is 39% higher than the reaction in entry 4 of Table 2.1. The product derived from tertiary allylic alcohol **36** and **22** was isolated in 61% yield, but no CM was observed in the reaction of **36** with **27**. The only reaction with **27** that was similar to that with **19** or **22** was the reaction in entry 1. Vinyl boronate **19** reacted with **7**

to form the cross product in 60% yield, and the use of **27** (entry 1) only decreased the yield by 2%. It is obvious that a large difference in reactivity exists between the vinyl boronates with and without an internal methyl group.

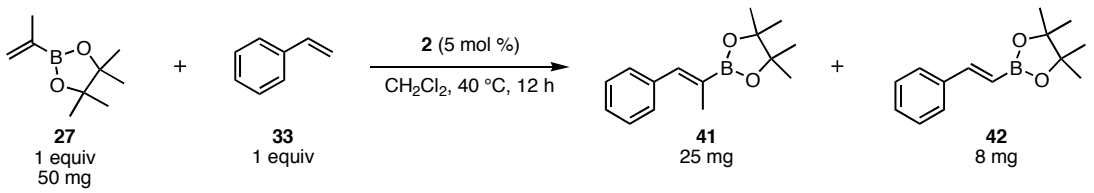
Substrates with groups larger than methyl at the α-position were synthesized by Christie Morrill and used in CM reactions (Scheme 2.7).[14,16] In those cases, yields were lower than reactions with **27**, and small changes to the starting materials often resulted in large reactivity differences. Although these compounds would be difficult to access regioselectively using internal alkyne hydroboration, the low yields and low *Z*:*E* selectivities observed in most of these reactions do not make CM a general, practical approach to synthesizing trisubstituted vinyl boronates.



Scheme 2.7. CM reactions with other α-substituted vinyl pinacol boronates.

In addition to unreacted starting materials, homocoupled cross partners, and the desired trisubstituted vinyl boronates, 1,2-disubstituted vinyl boronates were often formed during the course of the CM reactions described above. For example, in the reaction between **27** and styrene (**33**), a small amount of 1,2-disubstituted vinyl boronate **42** was present (Scheme 2.8). Upon closer inspection of the ^{1}H NMR spectrum and GC-MS of **27**, there was approximately 5% of **22** contaminating **27**. Assuming 5% contamination of **27** with **22**, the maximum yield of **42** was 3.4 mg in the reaction in

Scheme 2.8, but more than twice that amount was present. Was this due to a lack of quantitative accuracy in determining the amount of **22** in **27**, or was there an isomerization that shifted the methyl group from the internal position to the terminal position of the olefin prior to CM?



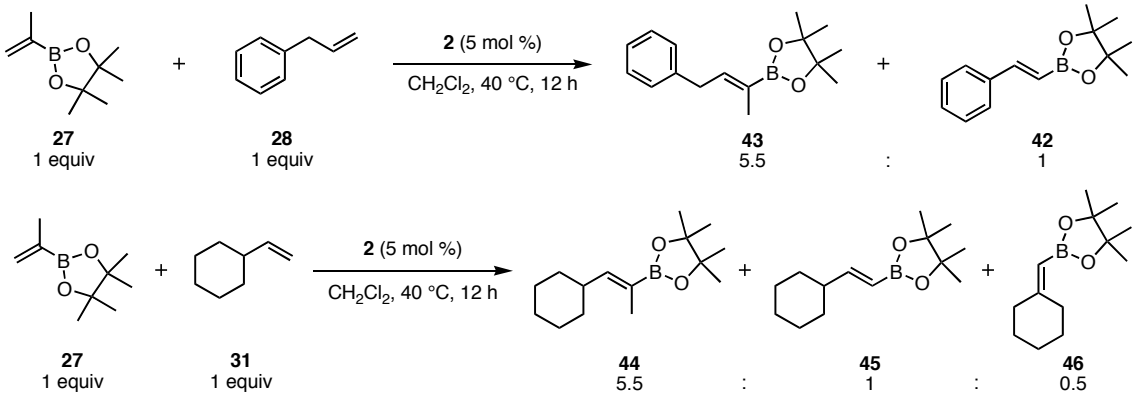
Scheme 2.8. Possible isomerization of **27** during CM.

The presence of a demethylated product was not unique to the reaction shown in Scheme 2.8. 1,2-Disubstituted vinyl boronates were observed in the CM reactions with allylbenzene (**28**), allyltrimethylsilane (**29**), allyltriisopropylsilane (**30**), vinylcyclohexane (**31**), and vinylcyclopentane (**32**). In all of these cases only small amounts of the 1,2-disubstituted products were present, but it was often greater than 100% yield based on the amount of **22** contaminating **27**, suggesting a methyl group shift was occurring. Unfortunately, the 1,2-disubstituted products were never separated from other byproducts due to the similarities in polarity, so isolated yields were never obtained. Although 1,2-disubstituted vinyl boronates were not formed by CM when groups larger than methyl were in the α-position, migration of the alkyl group from the α-position to the β-position was observed in up to 20% yield.[16] That observation supports an isomerization pathway leading to the impurities, but the mechanism by which the alkyl group migrates is not known.

In an attempt to discover whether **27** was undergoing a methyl group loss (to form **19**) or migration (to form **22**), it was exposed to catalyst **2** under the normal reaction

conditions. After 12 h, the major component of the reaction mixture was **27**. Only 3% of **22** was present, and no **19** was observed. Interestingly, compound **42** was present in 5% relative to **27**, but no **41** had formed. Presumably **42** originates from the reaction of either **22** or **19** with the benzylidene on catalyst **2**. The fact that no **41** was formed suggests that catalyst **2** reacts much more readily with terminal or 1,2-disubstituted vinyl boronates than with 1,1-disubstituted vinyl boronates. The small amount of **22** and **42** in this reaction (8%, more than the expected 5% based on the contamination of **27**) suggests that methyl group migration can occur and is dependent on the cross partner.

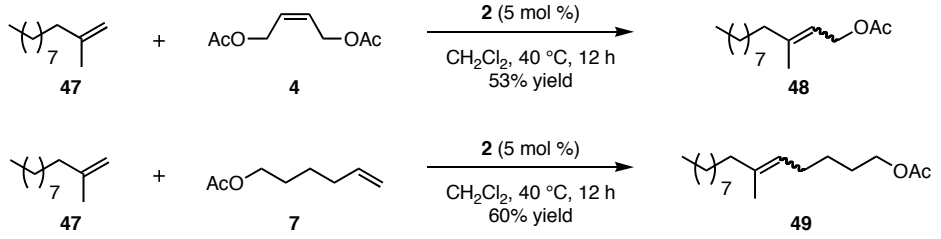
In addition to methyl and alkyl group migrations, olefin isomerization was also observed. For example, when both allylbenzene (**28**) and vinylcyclohexane (**31**) were used as cross partners, products arising from alkene-isomerization and/or methyl migration CM were observed (Scheme 2.9). In the reaction of vinylcyclopentane (**32**) with **27**, a mixture of products analogous to those obtained with vinylcyclohexane (**31**) was formed. A ruthenium hydride, formed by catalyst decomposition, could have caused the olefin isomerizations.[17]



Scheme 2.9. Complex product mixture arising from olefin isomerizations and methyl migrations.

It was not completely surprising that these reactions were plagued by low yields and complications. Although catalyst **2** is one of the most reactive, ruthenium-based,

olefin metathesis catalysts known, it does not readily catalyze the synthesis of trisubstituted alkenes by CM. In cases where trisubstituted olefins are formed, at least one of the substituents on the 1,1-disubstituted alkene is a methyl group (Scheme 2.10).[18] There are certain examples where trisubstituted olefins are formed in yields ≥80%, but typically it is not a reliable reaction and has not found widespread use in synthetic organic chemistry. In order for this reaction to become practical, a more active olefin metathesis catalyst is needed.



Scheme 2.10. CM reactions to form trisubstituted olefins.

Conclusion

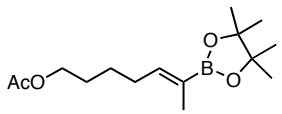
Vinyl boronates are versatile functional groups that can take part in many powerful synthetic transformations, and cross-metathesis (CM) is a mild, efficient way to make 1,2-disubstituted vinyl boronates. Because current approaches to the formation of trisubstituted vinyl boronates suffer from regioselectivity issues, CM with 1,1-disubstituted vinyl boronates was explored as an alternative route. In some instances the desired products were formed in 58%–60% yield, but many reactions were plagued by low yields and complicated product mixtures, including alkyl group migrations and olefin isomerizations. The lack of success found here illustrates the need for a more active olefin metathesis catalyst that can form trisubstituted alkenes efficiently.

Experimental

General Experimental. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), multiplet (m), and broad (br). Spectroscopic data are provided for the major olefin isomer. For all vinylboronates reported the ^{13}C peak of the α-carbon is not observed due to the large quadrupolar effect of the attached boron nucleus.

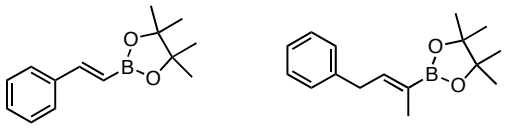
Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain or UV light. Flash column chromatography was performed using silica gel 60 (230–400 mesh). All glassware was either oven dried or flame dried, and reactions were done under an atmosphere of argon. All commercial chemicals were used as obtained except 1,4-diacetoxy-*cis*-2-butene (**4**), which was distilled from CaH_2. Benzene, methylene chloride, diethyl ether, and THF were dried by passage through solvent columns containing activated alumina.

General Cross-metathesis Procedure. To a solution of **2** (5 mol %) in CH_2Cl_2 (0.2 M in substrate) was added **27** (1 equiv) and cross partner (0.5–2 equiv), and the reaction stirred at 40 °C for 12 h. After rotary evaporation of the solvent, the remaining residue was purified by flash chromatography to afford the desired product (often as a mixture with other compounds).



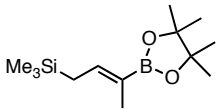
50

(*Z*)-6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hept-5-enyl acetate (50). Following the general procedure, **27** (100 mg, 0.60 mmol), **7** (48 μL, 42 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 49 mg (58% yield, >20:1 *Z*:*E*) of **50** (5% ethyl acetate in hexanes) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.28 (dt, J = 7.0, 1.6 Hz, 1H), 4.05 (t, J = 6.6 Hz, 2H), 2.14 (q, J = 7.4 Hz, 2H), 2.03 (s, 3H), 1.59–1.69 (m, 2H), 1.66 (s, 3H), 1.43–1.51 (m, 2H), 1.25 (m, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 145.8, 83.3, 64.6, 28.5, 28.3, 25.3, 25.0, 21.2, 14.1.

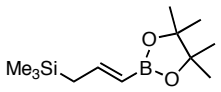


42 **43**

(*Z*)-4,4,5,5-Tetramethyl-2-(4-phenylbut-2-en-2-yl)-1,3,2-dioxaborolane (43). Following the general procedure, **27** (50 mg, 0.30 mmol), **28** (79 μL, 70 mg, 0.60 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 45 mg (59% yield, 7:1 *Z*:*E*) of **43** (3% ethyl acetate in hexanes) as a mixture with unreacted **27** and **42** (**43**:**27**:**42** = 5.5:1:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): (*Z*-isomer δ 7.17–7.32 (m, 5H), 6.49 (dt, J = 6.9, 1.6 Hz, 1H), 3.49 (d, J = 7.1 Hz, 2H), 1.82 (d, J = 0.8 Hz, 3H), 1.26 (s, 12H); **42**: 6.18 (d, J = 18.6, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 144.4, 140.7, 128.9, 128.6, 126.1, 83.4, 35.3, 25.0, 14.2.

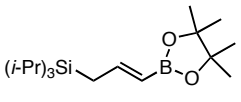


51

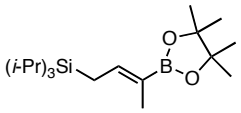


52

(*Z*)-Trimethyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enyl)silane (51). Following the general procedure, **27** (50 mg, 0.30 mmol), **29** (47 μL, 34 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1 mL CH_2Cl_2 afforded 45 mg (59% yield, >20:1 *Z*:*E*) of **51** (2% ethyl acetate in hexanes) as a mixture with unreacted **27** and **52** (**51**:**27**:**52** = 3.4:1:0.4). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.44 (tq, J = 8.8, 1.6 Hz, 1H), 1.66 (d, J = 8.8 Hz, 2H), 1.62–1.63 (m, 3H), 1.25 (s, 12H), 0.02 (s, 9H); **52**: 6.66 (dt, J = 18.0, 8.1 Hz, 1H).

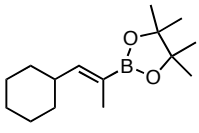


21

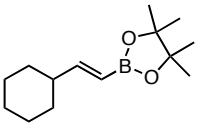


53

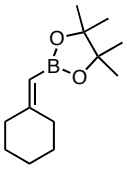
(*Z*)-Triisopropyl(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enyl)silane (53). Following the general procedure, **27** (50 mg, 0.30 mmol), **30** (72 μL, 59 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 60 mg (60% yield, >20:1 *Z*:*E*) of **53** (2.5% ethyl acetate in hexanes) as a mixture with unreacted **27** and **21** (**53**:**27**:**21** = 5:1:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.53 (tq, J = 8.8, 1.6 Hz, 1H). 1.72 (d, J = 8.9 Hz, 2H), 1.69 (d, J = 1.6 Hz, 3H), 1.23 (s, 12H), 1.04 (s, 18H); **21**: 6.75 (dt, J = 17.9, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 144.6, 83.0, 24.9, 18.9, 14.0, 13.9, 11.5.



44

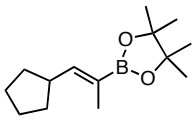


45

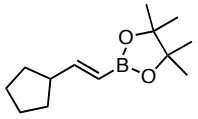


46

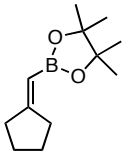
(*Z*)-2-(1-Cyclohexylprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (44). Following the general procedure, **27** (50 mg, 0.30 mmol), **31** (41 μL, 33 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 33 mg (44% yield, >20:1 *Z*:*E*) of **44** (2% ethyl acetate in hexanes) as a mixture with unreacted **27**, **45**, and **46** (**44**:**27**:**45**:**46** = 3.3:1:0.8:0.2). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.12 (dd, J = 8.8, 1.6 Hz, 1H), 1.68 (d, J = 1.6, 3H), 1.58–1.74 (m) 1.03–1.34 (m), 1.26 (s, 12H); **45**: 6.58 (dd, J = 18.1, 6.6 Hz, 1H); **46**: 5.01 (s, 1H).



54

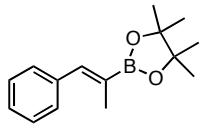


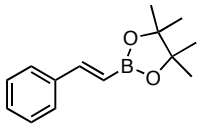
55



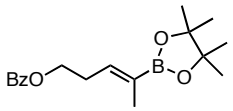
56

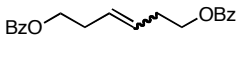
(*Z*)-2-(1-Cyclopentylprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (54). Following the general procedure, **27** (50 mg, 0.30 mmol), **32** (41 μL, 29 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 10 mg (14% yield, >20:1 *Z*:*E*) of **54** (2% ethyl acetate in hexanes) as a mixture with unreacted **27**, **55**, and **56** (**54**:**27**:**55**:**56** = 1:3:0.4:1). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.24 (tq, J = 8.8, 1.6 Hz, 1H), 1.70 (d, J = 1.6 Hz, 3H), 1.50–1.80 (m), 1.20–1.28 (m), 1.25 (s, 12H); **55**: 6.61 (dd, J = 18.1, 7.1 Hz, 1H); **56**: 5.27 (quint, J = 1.6 Hz, 1H).


41

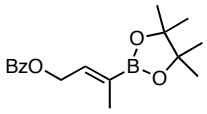

42

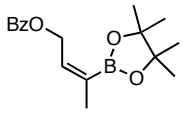
(*Z*)-4,4,5,5-Tetramethyl-2-(1-phenylprop-1-en-2-yl)-1,3,2-dioxaborolane (41). Following the general procedure, **27** (50 mg, 0.30 mmol), **33** (68 μL, 62 mg, 0.60 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 25 mg (34% yield, >20:1 *Z*:*E*) of **41** (2% ethyl acetate in hexanes) as a mixture with unreacted **27** and **42** (**41**:**27**:**42** = 1.4:1:0.5). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.21–7.40 (m, 6H), 2.00 (d, J = 1.6 Hz, 3H), 1.28 (s, 12H); **42**: 6.17 (d, J = 18.4 Hz, 1H).


57


58

(*Z*)-4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)pent-3-enyl benzoate (57). Following the general procedure, **27** (50 mg, 0.30 mmol), **34** (50 μL, 52 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded 43 mg (46% yield, >20:1 *Z*:*E*) of **57** (5% ethyl acetate in hexanes) as a mixture with **58** (**57**:**58** = 1:0.24). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.00–8.06 (m, 2H), 7.51–7.58 (m, 1H), 7.39–7.46 (m, 2H), 6.36 (tq, J = 7.1 Hz, 1.6 Hz, 1H), 4.36 (d, J = 7.1 Hz, 2H), 2.62 (observed q (actually a dt), J = 7.1 Hz, 2H), 1.75 (br s, 3H), 1.26 (s, 12H); **58**: 5.64–5.66 (m, 2H).


Z-59


E-59

(*Z* and *E*)-3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)but-2-enyl benzoate (*Z*-59) and (*E*-59). Following the general procedure, **27** (100 mg, 0.60 mmol), **35** (88 mg, 0.30 mmol), and **2** (12.6 mg, 0.015 mmol) in 1.5 mL CH_2Cl_2 afforded a total of 46 mg

(30% yield, 2:1 *Z*:*E*) of ***Z*-59** and ***E*-59** (4% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$, ppm) ***Z*-59**: δ 8.05–8.08 (m, 2H), 7.53–7.59 (m, 1H), 7.41–7.46 (m, 2H), 6.47 (tq, J = 5.9, 1.8 Hz, 1H), 4.98 (dd, J = 5.9, 0.9 Hz, 2H), 1.81 (dd, J = 1.8, 0.9 Hz, 3H), 1.28 (s, 12H); ***E*-59**: 8.05–8.08 (m, 2H), 7.52–7.57 (m, 1H), 7.41–7.46 (m, 2H), 6.26 (t, J = 5.9 Hz, 1H), 5.13 (dd, J = 6.4, 1.4 Hz, 2H), 1.86 (d, J = 1.4 Hz, 3H), 1.30 (s, 12H).

References

[1] (a) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100–110. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956. (c) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003.

[2] Chatterjee, A. K. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2, Chapter 2.8.

[3] (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. For CM with less active catalyst **1** see (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71, and references therein.

[4] For examples with catalyst **1**, see (a) Blechert, S., Brümmer, O.; Rückert, A. *Chem. Eur. J.* **1997**, *3*, 441–446. (b) Gibson, S. E.; Gibson, V. C.; Keen, S. P. *Chem. Commun.* **1997**, 1107–1108. (c) Gibson, S. E.; Biagini, S. C. G.; Keen, S. P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2485–2500. (d) Blechert, S.; Schuster, M.; Pernerstorfer, J. *Chem. Commun.* **1997**, 1949–1950.

[5] Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

[6] (a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171–3174. (b) Toste, F. D.; Chatterjee, A. K.; Grubbs, R. H. *Pure. Appl. Chem.* **2002**, *74*, 7–10. (c) Pietraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913–917. (d) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753.

[7] (a) Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187–190. (b) Goldberg, S. D.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 807–810.

[8] Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031–6034.

[9] (a) Brown, H. C.; Campbell, J. B., Jr. *Aldrichim. Acta* **1981**, *14*, 3–11. (b) Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286–3294.

[10] (a) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 5786–5788. (b) Brown, H. C.; Hamaoka, T.; Ravindran, N. *J. Am. Chem. Soc.* **1973**, *95*, 6456–6457.

[11] (a) Brown, H. C.; Bhat, N. G. *J. Org. Chem.* **1988**, *53*, 6009–6013. (b) Brown, H. C.; Basavaiah, D.; Kulkarni, S. U.; Bhat, N. G.; Vara Prasad, J. N. V. *J. Org. Chem.* **1988**, *53*, 239–246. (c) Miyaura, N. Organoboron Compounds. *Top. Cur. Chem.* **2002**, *219*, 11–59.

[12] Beletskaya, I.; Pelter, A. *Tetrahedron* **1997**, *53*, 4957–5026.

[13] (a) Zaidlewicz, M.; Meller, J. *Main Group Met. Chem.* **2000**, *23*, 765–772. (b) Tucker, C. E.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57*, 3482–3485. (c) Brown, H. C.; Gupta, S. K. *J. Am. Chem. Soc.* **1972**, *94*, 4370–4371. (d) Pereira, S.; Srebnik, M. *Organometallics* **1995**, *14*, 3127–3128. (e) Pelter, A.; Smith, K.; Buss, D.; Norbury, A. *Tetrahedron Lett.* **1991**, *32*, 6239–6242. (f) Brown, H. C.; Larock, R. C.; Gupta, S. K.; Rajagopalan, S.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6079–6084.

[14] A portion of the work described in this chapter is published: Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett*. **2004**, *45*, 7733–7736.

[15] For references that support oxygen chelation to Ru during metathesis, see (a) Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem. Int. Ed.* **2001**, *40*, 1277–1279, and references therein. (b) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett*. **2001**, *3*, 2209–2212. (c) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168–8179.

[16] Morrill, C. Ph.D. Thesis, California Institute of Technology, 2005.

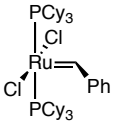
[17] Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc*. **2004**, *128*, 7414–7415.

[18] (a) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett*. **2002**, *4*, 1939–1942. (b) ref. 6d.

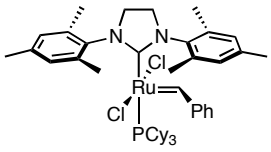
Chapter 3
Chemoselective Conjugated Diene Cross-Metathesis

Introduction

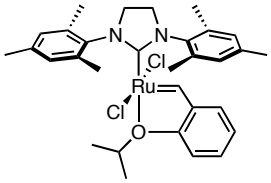
As discussed in the previous chapter, olefin cross-metathesis (CM) appears to be a straightforward, reliable method for the intermolecular coupling of two olefins. In reality, complications often arise due to the similar reactivities of simple olefins, especially when a highly active catalyst (such as **2**, **3**, or **4**) is used.[1] The formation of undesired homocoupled products can be diminished by increasing the steric bulk around the alkene or by reducing its electron density. Substitution in the allylic position causes products to be enriched in the desired heterocoupled olefin, but alkenes with substitution directly on the double bond (i.e., 1,1-disubstituted olefins) do not react efficiently in CM reactions with **2** or **3**, and yields are typically reduced relative to monosubstituted terminal olefins.[2] The low yields obtained for trisubstituted vinyl boronate formation presented in chapter 2 support this generalization.



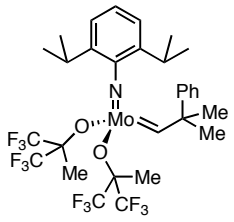
1



2



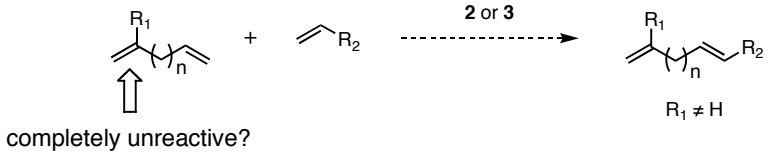
3



4

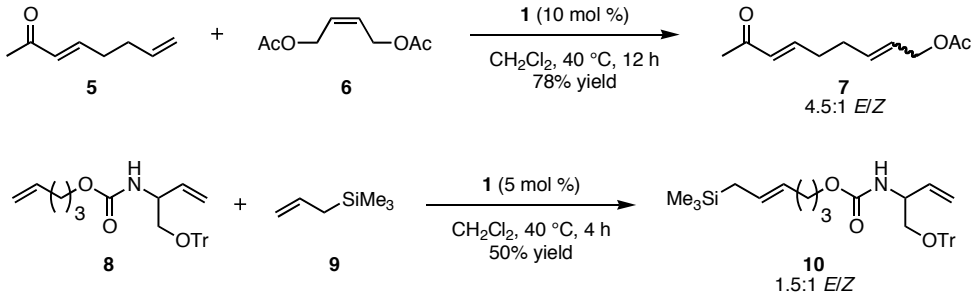
Although trisubstituted vinyl boronate synthesis by CM was only moderately successful, the lack of reactivity of catalyst **2** toward 1,1-disubstituted olefins suggested it could be used in chemoselective CM reactions. If a substrate containing both a monosubstituted terminal olefin and a 1,1-disubstituted olefin was used in a CM reaction,

catalyst **2** should react preferentially with the monosubstituted alkene (Scheme 3.1). A reaction of this type could have great synthetic potential.

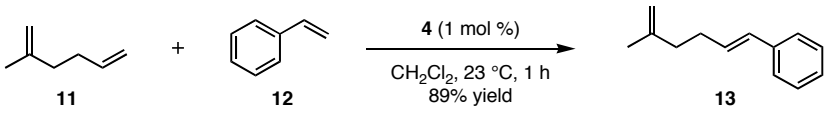


Scheme 3.1. Proposed chemoselective CM using a ruthenium catalyst.

Chemoselective CM had been previously achieved with catalysts **1** and **4** prior to this work. For example, catalyst **1** does not react efficiently with electron-poor olefins or with allylic amines, so it was used to selectivity react with unhindered terminal alkenes in the reactions illustrated in Scheme 3.2. In the upper reaction, the alkene in conjugation with the ketone does not react;[1a] in the lower reaction, the less hindered terminal olefin undergoes CM selectively.[3] Alkenes that are 1,1-disubstituted do not react with catalyst **4**, so a selective CM was achieved using **11** and styrene (**12**) (Scheme 3.3).[4] The latter reaction, which used a molybdenum catalyst instead of a ruthenium catalyst, is almost identical to the proposed chemoselective CM.

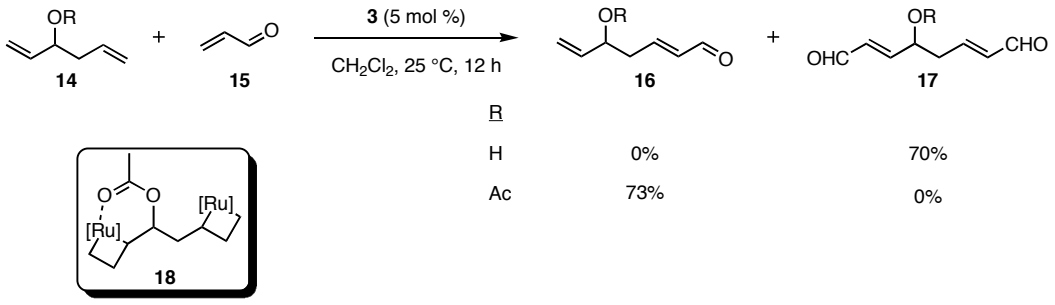


Scheme 3.2. Chemoselective CM using catalyst **1**.



Scheme 3.3. Chemoselective CM using catalyst **4**.

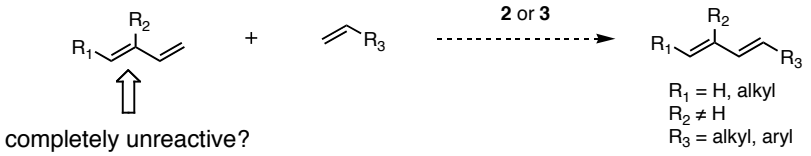
The reactions shown in Schemes 3.2 and 3.3 were successful because a catalyst was chosen that was known to be unreactive toward one of the olefins. Catalyst **1** was a reliable choice for chemoselective CM due to its low reactivity. On the other hand, catalysts **2** and **3** are significantly more reactive than **1**, and chemoselective CM is expected to be more challenging. When the research described in the current chapter began, there was only one report on chemoselective CM using N-heterocyclic carbene (NHC)-containing ruthenium metathesis catalysts.[5,6] Two olefins were present in the substrate (**14**): one had an alcohol or acetate in the allylic position, and the other alkene had an alcohol or acetate in the homoallylic position. When the alcohol was unprotected, CM occurred at both olefins using catalyst **3** (Scheme 3.4). If the alcohol was protected with an acetate group, CM occurred selectively at the homoallylic olefin. It was proposed that the deactivation of the allylic alkene was due to either the electron-withdrawing capability of the acetate group or to the formation of a stabilized, non-reactive complex (**18**). Steric hindrance was not thought to play a role in the selectivity.



Scheme 3.4. Chemoselective CM using a highly active ruthenium catalyst.

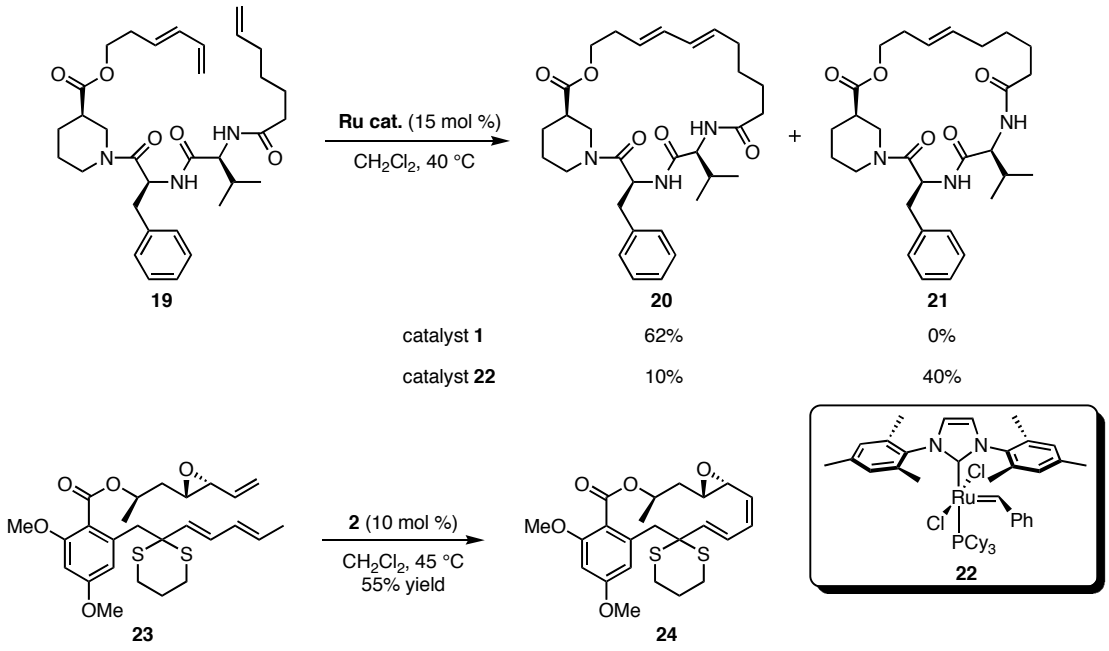
It is obvious from the examples above that chemoselective CM is a useful tool in accessing certain α,ω-dienes. Conjugated dienes, which are a category of substrates that fit the reaction proposed in Scheme 3.1, are found in natural products and are useful synthetic intermediates. Chemoselective CM could be used to form substituted

conjugated dienes as long as there is a substituent in an appropriate position to decrease the reactivity of one of the olefins (Scheme 3.5). Because ruthenium-catalyzed CM is mild and experimentally simple, chemoselective conjugated diene CM would be a synthetically valuable reaction.



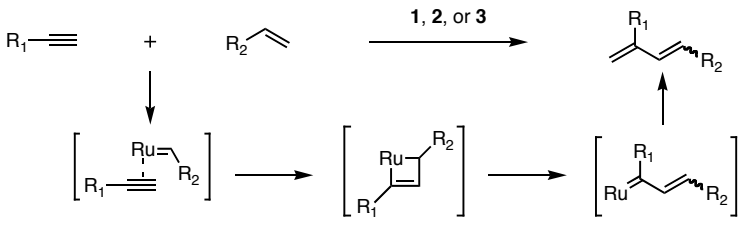
Scheme 3.5. Proposed chemoselective CM reaction of 2-substituted and 1,2-disubstituted 1,3-butadienes.

Conjugated diene olefin metathesis had been used in several natural product syntheses prior to the start of the work described here. In all cases, a macrocycle was formed using conjugated diene ring-closing metathesis (RCM) (Scheme 3.6). The Nolan group used the less active catalyst **1** to couple the two terminal olefins of substrate **19**; the more active compound **22** catalyzed metathesis at both olefins of the conjugated diene.[7] Danishefsky used catalyst **2** to form **24**, an advanced intermediate in the synthesis of radicicol and monocillin.[8] Because of the steric bulk around the internal alkene of the conjugated diene, olefin metathesis occurred exclusively between the two terminal olefins in the latter example. 1,1-Disubstituted alkenes were not present in any of these reactions.



Scheme 3.6. Conjugated diene RCM in natural product synthesis.

Enyne metathesis is another approach to the synthesis of conjugated dienes using olefin metathesis catalysts (Scheme 3.7).[9] Intramolecular enyne metathesis has been widely used to access natural products and diverse libraries of compounds. Intermolecular enyne metathesis (enyne CM) has been used less frequently than the intramolecular reaction. 2-Substituted conjugated dienes can be made using enyne CM with an alkyne and ethylene. When higher alkenes are used, products similar to those illustrated in Scheme 3.5 are formed. Unfortunately, catalyst loadings greater than 5%, low *E*/*Z* ratios of the products, and a large excess of the starting alkene decrease the synthetic practicality of this reaction.

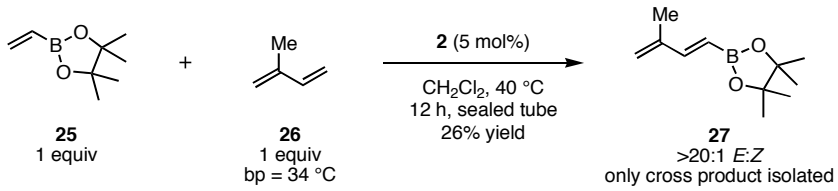


Scheme 3.7. Enyne CM and proposed mechanism.

Although a lot work had been done focusing on the synthesis of conjugated dienes using olefin metathesis, there were no examples where a chemoselective CM reaction was used to form conjugated dienes as shown in Scheme 3.5. Conjugated dienes are used as synthetic intermediates and are present in many natural products. Additionally, olefin metathesis is a mild, catalytic synthetic method that has found widespread use in organic chemistry. For these reasons, chemoselective conjugate diene CM was explored.

Results and Discussion[10]

The first reaction that was attempted was a CM between vinyl pinacol boronate (**25**) and isoprene (**26**) (Scheme 3.8). Isoprene has a boiling point of 34 °C, which is below the typical reaction temperature for vinyl boronate cross-metathesis, so the reaction was performed in a sealed tube. Although **27** was formed in only 26% yield, it was the only cross-metathesis product found in the reaction mixture. There was no product resulting from a reaction at the 1,1-disubstituted alkene, and only the *E*-isomer was formed.

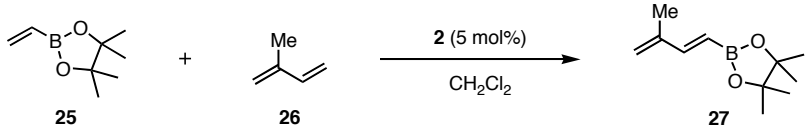


Scheme 3.8. Chemoselective conjugated diene CM to form a single product.

A variety of other reaction conditions were employed in the CM between **25** and **26**, but the yield was never higher than 48% (Table 3.1). One of the major driving forces for CM is the release of ethylene, and in a sealed tube, the ethylene remains present. Performing the reaction in an open flask did not increase the yield, even when isoprene

(**26**) was used as the solvent. The reaction was run under an atmosphere of ethylene to see if that would improve the yield, but it appeared to not affect the reaction at all.[11] In all of the conditions screened, the only product formed was **27**.

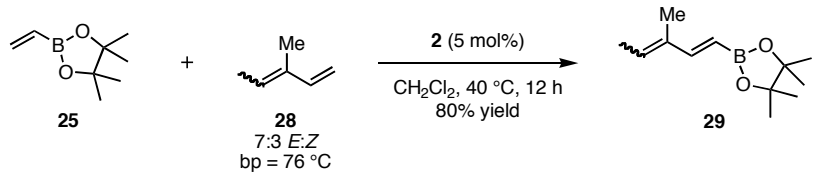
Table 3.1. CM of vinyl pinacol boronate and isoprene using catalyst **2**.



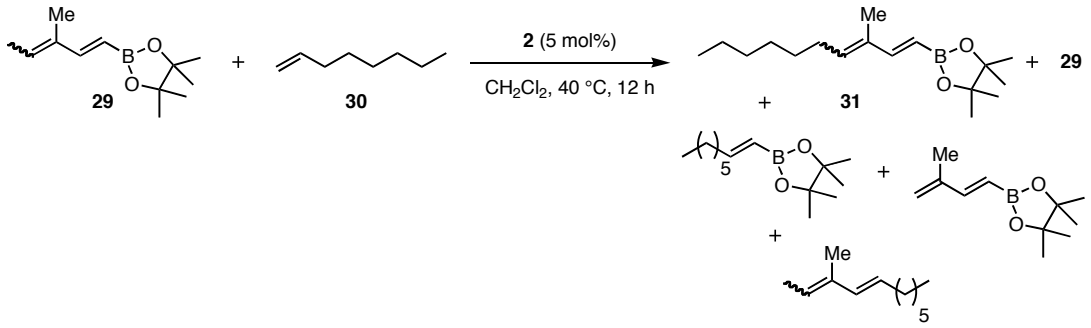
25 + **26** → **27**

Entry	25:26 (Equiv)	Type of Flask	Temp (°C)	Yield (%)
1	1:1	Sealed tube	40	26
2	1:2	Flask with condenser	32	34
3	1:4	Flask with condenser	40	<5
4	1:31 (solvent)	Flask with condenser	30	<5
5	1:2	Sealed tube	40	48
6	2:1	Sealed tube	40	22
7	1:1 (ethylene atm)	Sealed tube	40	26

The low boiling point of isoprene may have prevented high yields, so a higher boiling conjugated diene was used. Vinyl boronate **25** underwent chemoselective and diastereoselective CM with commercially available 3-methyl-1,3-pentadiene (**28**) to afford **29** in 80% isolated yield (Scheme 3.9). Compound **28** was used as a 7:3 *E*/*Z* mixture of isomers, and both isomers reacted. Only the *E*-isomer of the alkene formed in the CM reaction was observed. It was thought that once the vinyl boronate was crossed onto the diene, the new vinyl boronate olefin would be unreactive to further metathesis. Compound **29** was exposed to 1-octene (**30**) and more **2**, with the aim of producing **31**, which would come from a CM with the more substituted olefin of the diene (Scheme 3.10). Unfortunately a mixture of products, identified by ^{1}H NMR spectroscopy and GC-MS, was formed, and **31** was only present in <5%, indicating that the boronate-substituted alkene could still react.

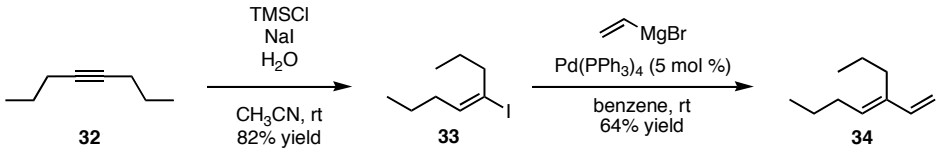


Scheme 3.9. CM of a 1,2-disubstituted 1,3-butadiene.



Scheme 3.10. Attempt to further functionalize **29** with CM.

Because the reaction with **28** was successful, another 1,2-disubstituted conjugated diene was made (Scheme 3.11). 4-Octyne (**32**) was reacted with an acetonitrile solution of HI generated in situ, and vinyl iodide **33** was isolated in 82% yield as a single stereoisomer.[12] A palladium-catalyzed Kumada coupling was used to form the conjugated diene **34** in 64% yield, also as a single stereoisomer.[13] This compound was stable for months in the refrigerator.

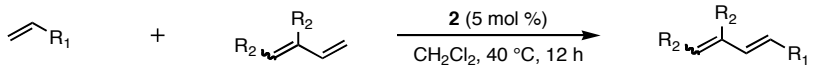


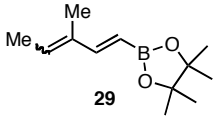
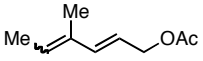
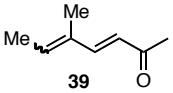
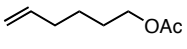
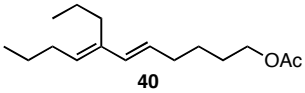
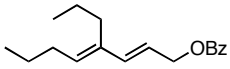
Scheme 3.11. Synthesis of substituted conjugated diene **34**.

With 1,2-disubstituted-1,3-butadienes **28** and **34** in hand, reactions with a number of different alkenes were explored (Table 3.2). 1,4-Diacetoxy-*cis*-2-butene (**6**) reacted with diene **28** in good yield to form an allyl-substituted conjugated diene (entry 2). Methyl vinyl ketone, an electron-poor olefin, also reacted with **28** to form a highly

conjugated molecule (entry 3). Diene **34** reacted similarly to **28**, and the CM reactions afforded products that were isolated in >75% yield. Only the *E*-isomers of all products were formed.

Table 3.2. CM reactions of 1,2-disubstituted 1,3-butadienes.

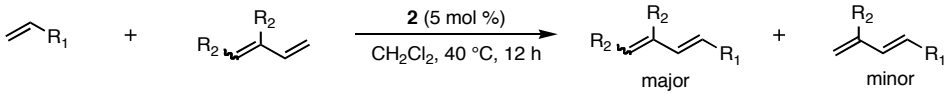


Entry	Alkene (equiv)	Diene[a]	Product	Yield (%)[b]	CH_2-Terminated Product (%)
1	**25** (1 equiv)	**28**	 **29**	80	10
2	 **6** (2 equiv)	**28**	 **38**	82	9
3	 **35** (1 equiv)	**28**	 **39**	70	7
4[c]	 **36** (4 equiv)	**34**	 **40**	77	12
5[d]	 **37** (2 equiv)	**34**	 **41**	79	0

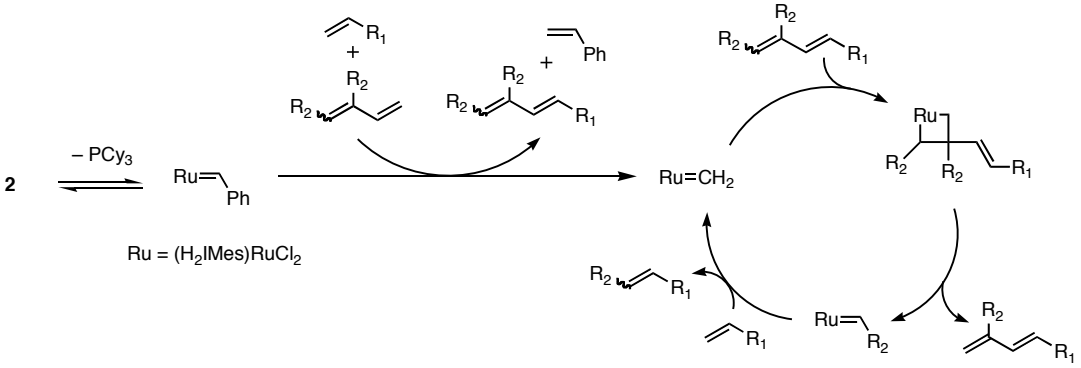
[a] Diene **28** was used as a 70:30 *E*/*Z* mixture. [b] Only the *E*-isomer of the products was observed in all cases; when diene **28** was used, both isomers reacted. [c] Product not separated from unreacted **36**. [d] Product not separated from allyl benzoate formed in reaction.

In addition to the desired products that were isolated in the reactions shown in Table 3.2, a minor impurity was often observed in the ^{1}H NMR spectrum. Ultimately it was determined that the impurity was the desired CM product where the alkyl group in the 1-position had been replaced with an H atom (Scheme 3.12). The far right column in Table 3.2 shows the amount of CH_2-terminated product that was present in each reaction. This product must originate from the formation of a ruthenium methylidene, which reacts with the more substituted olefin of the conjugated diene (Scheme 3.13). CM between the

methylidene and the hindered alkene of the diene could occur before or after the less-hindered olefin reacts with the cross partner. The amount of impurity is higher when an alkene that homocouples readily (i.e., **36**) is used, presumably because excess ethylene is formed. None of the product derived from CM between the alkene and the trisubstituted olefin of the conjugated diene was ever observed.



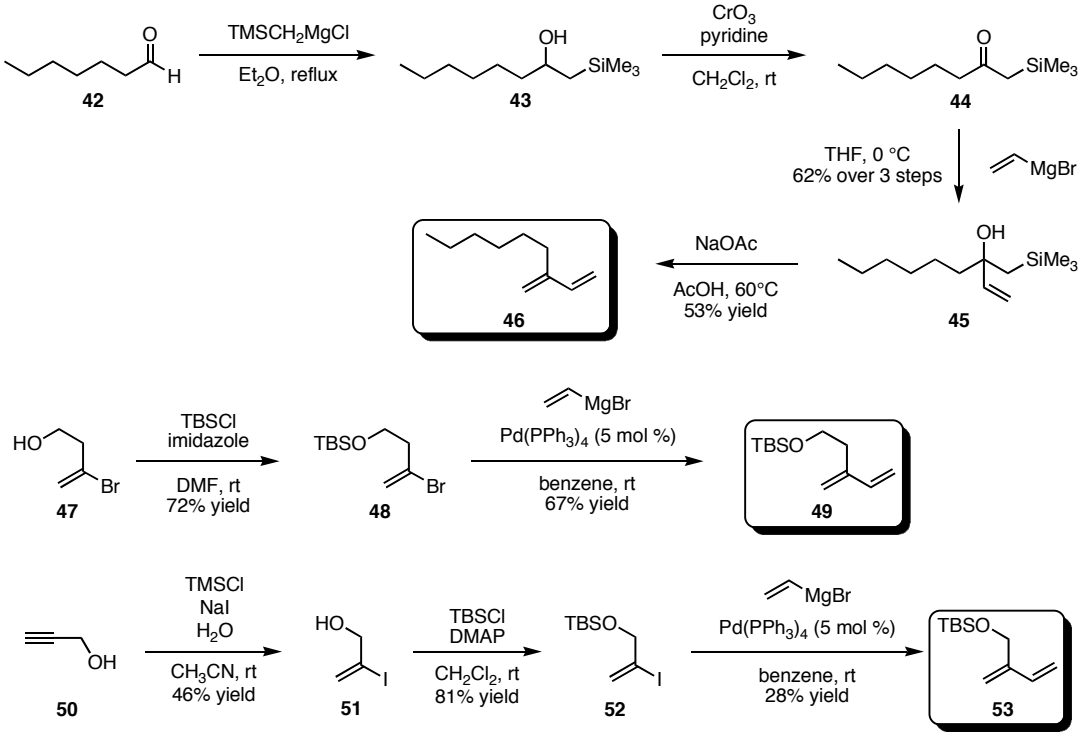
Scheme 3.12. Conjugated diene CM and the CH_2-terminated impurity.



Scheme 3.13. A proposed pathway leading to CH_2-terminated impurity.

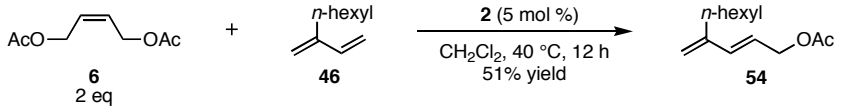
Conjugated diene CM was a success with 1,2-disubstituted 1,3-butadienes. The reactions were chemoselective with respect to the alkene cross partner, and only the *E*-isomer was isolated in all cases. But the question still remained as to whether the reaction would be successful with 2-substituted 1,3-butadienes. CM with isoprene was only moderately successful, and the low yields were attributed to the low boiling point of the diene. Therefore, 2-substituted 1,3-butadienes with higher boiling points were synthesized and used in CM. The syntheses of three conjugated dienes used in this study are shown in Scheme 3.14. Diene **46** was made in a four-step synthesis that was a modification of a known procedure.[14] The Collins oxidation to form **44** was very rapid,

and the α-silyl ketone was not stable under the reaction conditions, so the reaction mixture was filtered through silica within 1 minute after addition of **43**. Purification was not needed until after the third step. Silyl ether **48** reacted with vinyl magnesium bromide in the presence of a palladium catalyst to afford diene **49**.[13] Compound **53** was synthesized in a sequence similar to that of **49**. The Kumada coupling was low yielding, possibly due to elimination of the vinyl iodide or magnesium-iodide exchange.



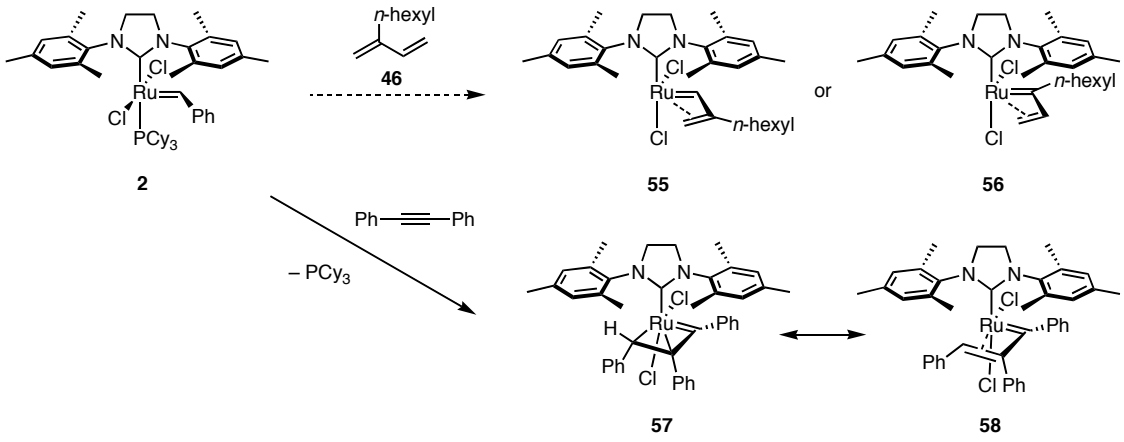
Scheme 3.14. Synthesis of three conjugated dienes.

The first CM reaction with a 2-substituted 1,3-butadiene that was explored was between **46** and **6** (Scheme 3.15). When the same conditions used for the other conjugated diene CM reactions were employed, the desired product was isolated in 51% yield. The reaction was completely chemoselective, and only the *E*-isomer was produced, but there was room for improvement regarding the yield.



Scheme 3.15. CM with **46** using standard conditions.

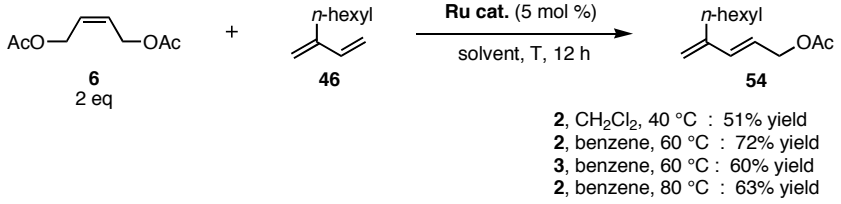
Unreacted **46** was present at the end of the reaction, which suggested that the catalyst may have been shut down before the CM was complete. If the conjugated diene reacted with the catalyst to form a vinyl alkylidene, intramolecular coordination of the alkene may have formed a stabilized, less active metathesis catalyst (Scheme 3.16, compounds **55** and **56**). A ruthenium complex with a similar structure has been reported.[15] The reaction of diphenylacetylene with **2** forms a metathesis-inactive ruthenium complex (**57**) that resembles a vinyl alkylidene acting as a bidentate or tridentate ligand. Additionally, yields for some enyne metathesis reactions can be drastically increased by performing the reaction under an atmosphere of ethylene, which has been proposed to break up coordination of the vinyl alkylidene formed during the catalytic cycle (see Scheme 3.7).[16]



Scheme 3.16. Stabilized intermediates potentially hindering conjugated diene CM reactions.

When the solvent was changed to benzene and the temperature of the CM reaction was increased to 60 °C, the desired conjugated diene product was formed in 72% yield

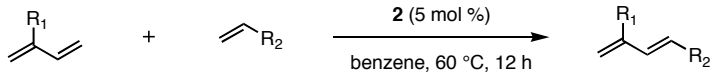
(Scheme 3.17). The elevated temperature may have weakened a ruthenium–alkene dative bond and allowed the stabilized ruthenium intermediate to reenter the catalytic cycle. Increasing the temperature to 80 °C resulted in a lower yield, potentially due to catalyst decomposition. Catalyst **2** afforded the conjugated diene in a higher yield than **3** under the same conditions. The increase in temperature did not affect the chemo- or stereoselectivity of the CM reaction; only one product was formed.

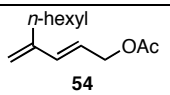
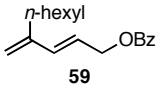
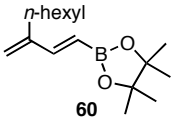
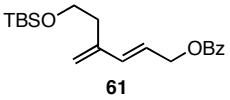
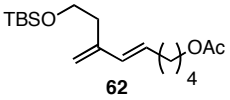
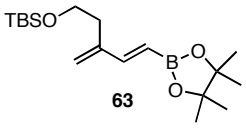
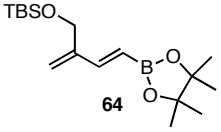
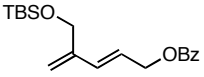


Scheme 3.17. Solvent and temperature effects in conjugated diene CM.

Using the modified reaction conditions, various 2-substituted 1,3-butadienes reacted with functionalized olefins to form the desired dienes in good yields with high chemo- and diastereoselectivity (Table 3.3). Only the *E*-isomer was observed in all of the reactions. Vinyl boronate **25** reacted cleanly with dienes **46** and **49**, as long as the reaction was stopped after 2 h (entries 3 and 6). Longer reaction times did not increase the yield, and an unidentified, inseparable impurity was formed. When **53** and **25** were reacted, the impurity was present even after 2 h (entry 7). Dienes **46** and **49** behaved similarly to each other in the CM reactions; yields were typically 70%–75%, and the reactions were clean. The yields decreased in reactions where the silyl ether functionality was separated from the diene by only one methylene (**53**). When **53** was used as a tetrahydropyranyl (THP)-protected alcohol, the desired dienes were formed in <40% yield. Unreacted diene was present at the end all of the CM reactions with 2-substituted 1,3-butadienes, but longer reaction times did not increase yields.

Table 3.3. CM with 2-substituted 1,3-butadienes.



Entry	Alkene (equiv)	Diene	Product[a]	Yield (%)[b]
1	**6** (2)	**46**	 **54**	72 (81)
2[c]	**37** (2)	**46**	 **59**	73
3[d]	**25** (2)	**46**	 **60**	73
4	**37** (2)	**49**	 **61**	70
5	**36** (4)	**49**	 **62**	75
6[d]	**25** (2)	**49**	 **63**	69
7[d,e]	**25** (2)	**53**	 **64**	~40
8	**37** (2)	**53**	 **65**	63

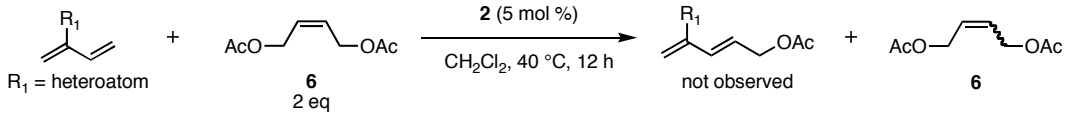
[a] Only the *E*-isomer of the product was observed. [b] Yield in parentheses refers to reaction with 10 mol % **2**. [c] Product not separated from allyl benzoate formed in reaction. [d] Reaction stopped after 2 h. [e] Unidentified impurities present in isolated product.

The reactions in Table 3.3 all required excess alkene to achieve good yields. Attempts to homocouple the 2-substituted 1,3-conjugated dienes were unsuccessful, which suggested that the CM reaction should be selective for the desired heterocoupled product.[17] If that were the case, only one or two equivalents of alkene should have been needed to access the desired diene in high yield, but 2–4 equivalents of the alkene must be used (2 equivalents of **6** and **37** are the same as 4 equivalents of allyl acetate and allyl

benzoate, respectively). The need for excess cross partner highlights the importance of not allowing the diene to react with the catalyst to form a vinyl alkylidene species. The higher concentration of reactive olefin can reduce the interaction between the catalyst and the diene.

All of the 2-substituted 1,3-butadienes in Table 3.3 have a carbon atom bound to the conjugated diene. Dienes with heteroatoms in the 2-position are important synthetic intermediates, so CM with this class of compounds was explored. Chloroprene (**66**), the trimethylsilyl enol ether of methyl vinyl ketone (**67**), and the triisopropylsilyl enol ether of methyl vinyl ketone (**68**) were reacted with 1,4-diacetoxy-*cis*-2-butene (**6**) under typical CM conditions (Table 3.4). None of the desired product was detected in any reaction, even when they were run at 60 °C in benzene.

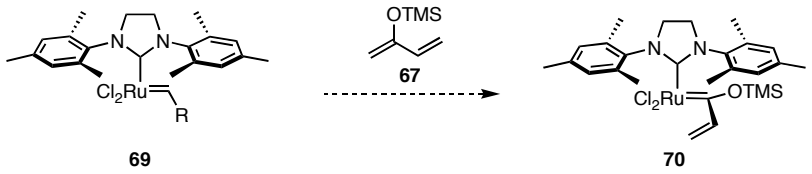
Table 3.4. Attempted CM reactions with heteroatom-substituted conjugated dienes.



Diene	*E*:*Z* ratio of 6
No diene	12 : 1
 **66**	1 : 2.7
 **67**	1 : 1.5
 **68**	2.8 : 1

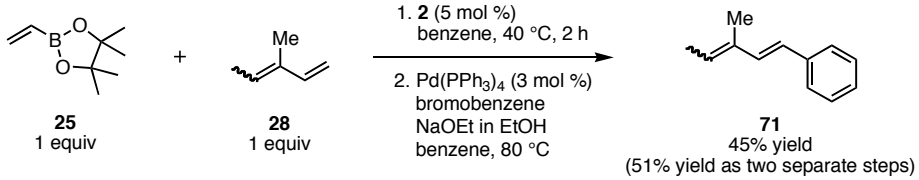
Insight into the fate of these reactions could be obtained by monitoring the amount of **6** that was isomerized. In the absence of another alkene, **6** was isomerized by **2** to a 12:1 *E*:*Z* mixture after 12 h at 40 °C in CH_2Cl_2. In the presence of dienes with

heteroatom substitution in the 2-position, **6** never completely isomerized, indicating catalyst decomposition. As the heteroatom substituent decreased in size, the amount of *E*-isomer formed also decreased. These data are consistent with the formation of a Fischer carbene by the reaction of a catalytically active ruthenium alkylidene with the more hindered olefin of the conjugated diene (Scheme 3.18). Ruthenium Fischer carbenes typically show greatly reduced metathesis activity, so any formed during this reaction exit the catalytic cycle.[18]



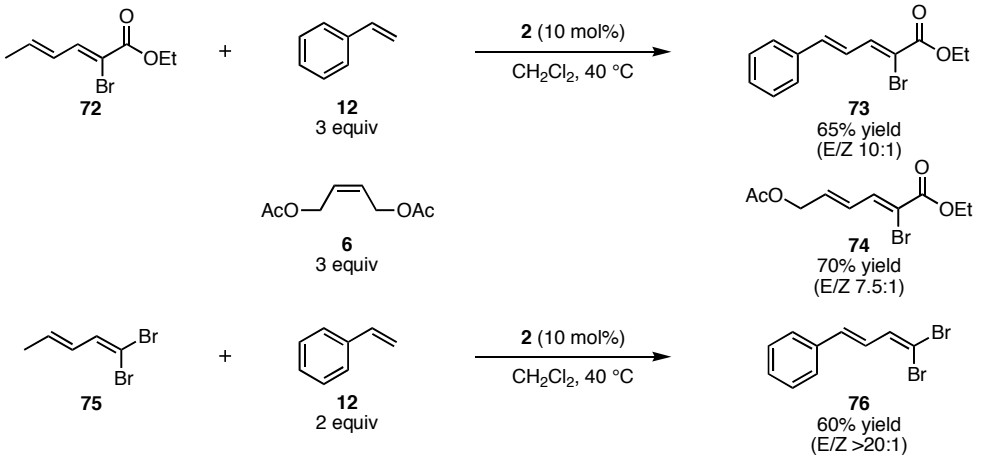
Scheme 3.18. Fischer carbene formed by **69** reacting with the silyl enol ether of **67**.

The conjugated dienes generated over the course of this study have the potential to be further functionalized, even without isolation. For example, dienes synthesized by enyne metathesis reactions have undergone [4 + 2]-cycloadditions without purification.[19] One of the unique features of this work is the formation of conjugated vinyl boronates, which are versatile functional groups. As illustrated in Scheme 3.19, a one-pot, chemoselective, conjugate diene CM/Suzuki coupling was successfully executed. The yield of this unoptimized reaction was similar to the two-step procedure, but no purification was needed after CM.



Scheme 3.19. One-pot conjugate diene CM/Suzuki coupling.

In addition to the 2-substituted and 1,2-disubstituted 1,3-butadienes discussed in this chapter, other conjugated diene CM has been explored in our lab by Dr. Jon Efskind.[10] Although the details of that work are beyond the scope of this chapter, a few sentences regarding it are warranted. It was thought that a combination of steric hindrance and electronic deactivation would render the trisubstituted alkenes of **72** and **75** unreactive to CM with catalyst **2**. This theory was tested, and CM occurred exclusively at the 1,2-disubstituted olefins (Scheme 3.20). The yields are only slightly reduced relative to most of the reactions discussed above, and the products have a variety of different functional group handles, making the products useful synthetic intermediates.



Scheme 3.20. Conjugated diene CM with 1,1-disubstituted 1,3-butadienes.

Conclusion

Conjugated dienes are important in organic chemistry as both constituents of natural products and synthetic intermediates. Therefore, the development of methods by which substituted conjugated dienes can be generated is crucial. Chemoselective cross-metathesis (CM) was successfully used to couple 2-substituted and 1,2-disubstituted 1,3-butadienes to a variety of functionalized alkenes. This technique took advantage of the

lack of reactivity between ruthenium olefin metathesis catalyst **2** and 1,1-disubstituted alkenes. Many of the conjugated dienes formed using this method contain functional groups that can undergo further manipulation, and it was discovered that a one-pot CM/Suzuki coupling reaction was possible. The simplicity of use and functional group tolerance of ruthenium metathesis catalysts, as well as the high chemo- and diastereoselectivity with which these transformations occurred, make this an attractive method for synthesizing functionalized conjugated dienes.

Experimental

General Experimental. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), multiplet (m), and broad (br). Spectroscopic data are provided for the major olefin isomer. For all vinylboronates reported the ^{13}C peak of the α-carbon is not observed due to the large quadrupolar effect of the attached boron nucleus. E/Z ratios given for the products indicate the ratios of the C=C bond formed in cross-metathesis and were determined from coupling constants of vinylic protons in the ^{1}H NMR spectrum.

Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stains or UV light. Flash column chromatography was performed using silica gel 60 (230–400 mesh). All glassware was

either oven dried or flame dried, and reactions were done under an atmosphere of argon. All commercial chemicals were used as obtained except 1,4-diacetoxy-*cis*-2-butene (**6**), which was distilled from CaH_2, and heptanal (**42**), which was distilled. 3-Methyl-1,3-pentadiene (**28**) was received (Aldrich) as a 70:30 mixture of E/Z isomers, and both isomers underwent cross-metathesis in the examples below (NMR spectral data are given for both isomers whenever they could be determined). Benzene, methylene chloride, diethyl ether, and THF were dried by passage through solvent columns containing activated alumina.

(*E*)-4,4,5,5-Tetramethyl-2-(3-methylbuta-1,3-dienyl)-1,3,2-dioxaborolane (27). To a solution of **2** (28 mg, 0.032 mmol) in 2 mL of CH_2Cl_2 in a pressure vessel was added isoprene (**26**) (130 μL, 89 mg, 1.3 mmol) and **25** (111 μL, 100 mg, 0.65 mmol). The vessel was sealed, and the reaction solution stirred at 40 °C. After 12 h at 40 °C, the solution was condensed, and the remaining residue was purified by flash chromatography (4% ethyl acetate in hexanes) to afford 49 mg of a 4:3 **27**:**25** mixture (31 mg of **27**, 48% yield). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.11 (d, J = 18.1 Hz, 1H), 5.56 (d, J = 18.1 Hz, 1H), 5.16 (s, 2H), 1.86 (s, 3H), 1.29 (s, 12H).

(*E*)-4-Iodooct-4-ene (33).[12] To a solution of sodium iodide (1.63 g, 10.9 mmol) in 20 mL of acetonitrile was added trimethylsilyl chloride (1.4 mL, 1.2 g, 11 mmol), followed by water (98 μL, 98 mg, 5.4 mmol). After 10 min at rt, 4-octyne (**32**) (1.3 mL, 1.0 g, 9.1 mmol) was added. After 1 h at rt, the solution was diluted with 25 mL of water and was extracted with Et_2O (3 × 40 mL). The combined organic layers were washed with

saturated aqueous $Na_2S_2O_3$ (2 × 40 mL), 40 mL of brine, dried over $MgSO_4$, and evaporated to an oil. Purification by flash chromatography (100% hexanes) afforded 1.77 g (82% yield) of **33** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.47 (tt, J = 6.9, 1.1 Hz, 1H), 2.44 (tq, J = 7.4, 1.1 Hz, 2H), 2.06–2.14 (m, 2H), 1.54 (sext, J = 7.4 Hz, 2H), 1.43 (sext, J = 7.4 Hz, 2H), 0.94 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H).

(*E*)-4-Vinyloct-4-ene (34).[13] To a solution of $Pd(PPh_3)_4$ (340 mg, 0.29 mmol) in 30 mL benzene at rt was added **33** (1.4 g, 5.9 mmol) and vinylmagnesium bromide (1M in THF, 11.8 mL, 11.8 mmol). After 3 h, saturated aqueous NH_4Cl was added and the mixture was extracted with 3 × 25 mL Et_2O. The organics were combined, washed with saturated aqueous $NaHCO_3$, water, brine, dried over $MgSO_4$, and concentrated. The crude oil was purified by flash chromatography (hexanes) to give 0.52 g (64% yield) **34** as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.68 (dd, J = 17.6, 11.0 Hz, 1H), 5.38 (t, J = 7.4 Hz, 1H), 5.21 (d, J = 17.9 Hz, 1H), 5.06 (dt, J = 11.0, 1.6 Hz, 1H), 2.11–2.19 (m, 4H), 1.34–1.57 (m, 4H), 0.91 (t, J = 7.4 Hz, 3H), 0.90 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.6, 133.2, 130.9, 113.0, 35.7, 29.6, 23.3, 22.1, 14.2, 14.0. HRMS (EI) calc. for $C_{10}H_{18}$: 138.1409, found 138.1406.

General Procedure for Cross-metathesis Reactions Using 1,2-Disubstituted 1,3-Butadienes (Table 3.2). Entry 1, 4,4,5,5-Tetramethyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dienyl)-1,3,2-dioxaborolane and 4,4,5,5-tetramethyl-2-((1*E*,3*Z*)-3-methylpenta-1,3-dienyl)-1,3,2-dioxaborolane (29). To a solution of **2** (14 mg, 0.016 mmol) in CH_2Cl_2 (1 mL) was added 3-methyl-1,3-pentadiene (**28**) (27 mg, 0.32 mmol) and vinylboronate

25 (50 mg, 0.32 mmol). The solution stirred at 40 °C for 12 h, and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (5% ethyl acetate:hexanes) to give 54 mg (80% yield, >20:1 E/Z) of the two isomers of **29**. A small amount (10%) of the cross product missing the terminal methyl group was identified by a broad singlet at 5.15 ppm in the ^{1}H NMR spectrum (terminal C=CH_2) and by HRMS (EI) (calc. for $C_{11}H_{19}BO_2$: 194.1478, found 194.1485). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.47 (d, J = 18.1 Hz, 1H, *Z*-isomer), 7.03 (d, J = 18.1 Hz, 1H, *E*-isomer), 5.76 (q, J = 6.8 Hz, 1H, *E*-isomer), 5.62 (m, 1H, *Z*-isomer), 5.55 (d, J = 18.1 Hz, 1H, *Z*-isomer), 5.42 (d, J = 18.1 Hz, 1H, *E*-isomer), 1.78 (d, J = 11.0 Hz, 3H), 1.73 (s, 3H), 1.26 (s, 12H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) of *E*-isomer: δ 154.7, 131.9, 129.1, 83.2, 25.0, 14.5, 11.5. HRMS (EI) calc. for $C_{12}H_{21}BO_2$ (for both isomers): 208.1635, found 208.1636 and 208.1627.

Entry 2, (2*E*,4*E*)-4-methylhexa-2,4-dienyl acetate and (2*E*,4*Z*)-4-methylhexa-2,4-dienyl acetate (38). Following the general procedure for **29**, 3-methyl-1,3-pentadiene (**28**) (40 mg, 0.49 mmol), 1,4-diacetoxy-*cis*-2-butene (**6**) (167 mg, 0.97 mmol), and **2** (21 mg, 0.024 mmol) in 1.5 mL CH_2Cl_2 gave 62 mg (82% yield, >20:1 E/Z) of **38** as a colorless oil. A small amount (9%) of the cross product missing the terminal methyl group was identified by a broad singlet at 5.00 ppm in the ^{1}H NMR spectrum (terminal C=CH_2) and by HRMS (EI) (calc. for $C_8H_{12}O_2$: 140.0837, found 140.0841). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.71 (d, J = 15.5 Hz, 1H, *Z*-isomer), 6.29 (d, J = 15.7 Hz, 1H, *E*-isomer), 5.44–5.77 (m, 2H, both *E*- and *Z*-isomers), 4.64 (d, J = 7.1 Hz, 2H, *Z*-isomer), 4.59 (d, J = 7.4 Hz, 2H, *E*-isomer), 2.06 (s, 3H, *Z*-isomer), 2.05 (s, 3H, *E*-isomer), 1.81

(d, J = 15.9 Hz, 3H, both isomers), 1.72 (s, 3H, *E*-isomer), 1.70 (s, 3H, *Z*-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) of *E*-isomer: δ 171.1, 139.8, 133.8, 128.8, 119.5, 65.7, 21.2, 14.1, 12.1. HRMS (EI) calc. for $C_9H_{14}O_2$ (for both isomers): 154.0994, found 154.0987 and 154.0994.

Entry 3, (3*E*,5*E*)-5-methylhepta-3,5-dien-2-one and (3*E*,5*Z*)-5-methylhepta-3,5-dien-2-one (39). Following the general procedure for **29**, 3-methyl-1,3-pentadiene (**28**) (40 mg, 0.49 mmol), methylvinylketone (**35**) (34 mg, 0.49 mmol), and **2** (21 mg, 0.024 mmol) in 1.5 mL CH_2Cl_2 gave 42 mg (70% yield, >20:1 E/Z) of **39** as a colorless oil. A small amount (7%) of the cross product missing the terminal methyl group was identified by a broad singlet at 5.40 ppm in the ^{1}H NMR spectrum (terminal C=CH_2) and by HRMS (EI) (calc. for $C_7H_{10}O$: 110.0732, found 110.0727). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.26 (d, J = 15.7 Hz, 1H, *Z*-isomer), 7.14 (d, J = 15.9 Hz, 1H, *E*-isomer), 6.15 (d, J = 15.9 Hz, 1H, *Z*-isomer), 6.05 (d, J = 15.9 Hz, 1H, *E*-isomer), 6.01 (q, J = 7.1 Hz, 1H, *E*-isomer), 5.88 (q, J = 7.1 Hz, 1H, *Z*-isomer), 2.32 (s, 3H, *Z*-isomer), 2.26 (s, 3H, *E*-isomer), 1.87–1.90 (m, 3H, *Z*-isomer), 1.83–1.87 (m, 3H, *Z*-isomer), 1.81 (d, J = 7.1 Hz, 3H, *E*-isomer), 1.76 (s, 3H, *E*-isomer). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) of *E*-isomer: δ 199.2, 148.8, 137.7, 134.3, 125.1, 31.8, 27.5, 22.9. HRMS (EI) calc. for $C_8H_{12}O$ (for both isomers): 124.0888, found 124.0882 and 124.0886.

Entry 4, (5*E*,7*E*)-7-propylundeca-5,7-dienyl acetate (40). Following the general procedure for **29**, diene **34** (40 mg, 0.29 mmol), 5-hexenyl acetate (**36**) (165 mg, 1.2 mmol), and **2** (12 mg, 0.014 mmol) in 1.2 mL CH_2Cl_2 gave 56 mg (77% yield, >20:1

E/Z) of **40** as a colorless oil. The product was not separated from unreacted **36** (1.0:0.32 **40**/**36**). A small amount (12%) of the cross product missing the terminal methyl group was identified by 2 broad singlets at 5.84 and 5.88 ppm in the ^{1}H NMR spectrum (terminal C=C*H*$_2$). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.31 (d, J = 15.7 Hz, 1H), 5.64 (dt, J = 15.7, 6.9 Hz, 1H), 5.24 (t, J = 7.1 Hz, 1H), 4.06 (t, J = 6.6 Hz, 2H), 2.06–2.19 (m, 6H), 2.04 (s, 3H), 1.58–1.70 (m, 2H), 1.38–1.52 (m, 6H), 0.89 (q, J = 6.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.4, 136.1, 129.2, 128.7, 127.0, 64.6, 36.5, 33.1, 29.6, 28.3, 26.1, 23.3, 22.2, 21.2, 14.2, 14.0. HRMS (EI) calc. for $C_{16}H_{28}O_2$: 252.2089, found 252.2094.

Entry 5, (2*E*,4*E*)-4-propylocta-2,4-dienyl benzoate (41). Following the general procedure for **29**, diene **34** (40 mg, 0.29 mmol), 1,4-dibenzoyl-2-butene (**37**) (171 mg, 0.58 mmol), and **2** (12 mg, 0.014 mmol) in 1.4 mL CH_2Cl_2 gave 62 mg (79% yield, >20:1 E/Z) of **41** as a colorless oil. The product was not separated from allyl benzoate formed in the reaction (1.0:0.25 **41**/allyl benzoate). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05–8.10 (m, 2H), 7.52–7.59 (m, 1H), 7.41–7.48 (m, 2H), 6.70 (dd, J = 15.8, 1.1 Hz, 1H), 5.88 (dt, J = 15.7, 6.3 Hz, 1H), 5.43 (t, J = 7.4 Hz, 1H), 4.91 (dd, J = 6.6, 1.1 Hz, 2H), 2.12–2.21 (m, 4H), 1.35–1.55 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H), 0.91 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.6, 135.4, 133.1, 132.1, 131.2, 129.8, 128.8, 128.5, 122.2, 66.5, 36.2, 29.7, 23.3, 22.0, 14.2, 14.0. HRMS (EI) calc. for $C_{18}H_{24}O_2$: 272.1776, found 272.1777.

3-((Trimethylsilyl)methyl)non-1-en-3-ol (45).[14] (Trimethylsilylmethyl)magnesium chloride (1.0 M in Et_2O, 15.8 mL, 15.8 mmol) was slowly added to a solution of heptanal (**42**) (1.8 mL, 1.5 g, 13 mmol) in 14 mL of Et_2O. After 1.5 h at 40 °C, the solution was carefully quenched with saturated aqueous NH_4Cl (20 mL) and was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with 50 mL of water, 50 mL of saturated aqueous $NaHCO_3$, 50 mL of brine, were dried over $MgSO_4$, and evaporated to 2.36 g of **43** a colorless oil that was used directly in the next reaction. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 3.74–3.84 (br m, 1H), 1.20–1.46 (m, 11H), 0.83–0.90 (m, 5H), 0.04 (s, 9H). To a solution of CrO_3 (7.88 g, 78.8 mmol) in 90 mL CH_2Cl_2 was added pyridine (7.7 mL, 7.5 g, 95 mmol), and the solution bubbled and became dark orange/red. After 40 min at rt, a solution of crude **43** (2.36 g, 11. 6 mmol) in 9 mL of CH_2Cl_2 was added to the orange/red solution. The color of the reaction immediately turned brown, and after 30 seconds, the mixture was filtered through a silica gel pad. *Longer reaction times led to product decomposition.* The silica gel pad was washed with Et_2O (50 mL), and the filtrate was evaporated to a brown oil. The oil was dissolved in Et_2O (40 mL), washed with 1 M aqueous $CuSO_4$ (2 × 25 mL), dried over $MgSO_4$, and evaporated to 2.13 g of **44** as a brown oil that was used directly in the next reaction. ^1H NMR (300 MHz, $CDCl_3$, ppm): δ 2.33 (t, J = 7.1 Hz, 2H), 2.20 (s, 2H), 1.49–1.56 (m, 2H), 1.24–1.30 (br m, 6H), 0.85–0.89 (m, 3H), 0.11 (s, 9H). Vinyl magnesium bromide (1.0 M in THF, 13 mL, 13 mmol) was added slowly to a solution of crude **44** (2.13 g, 10.6 mmol) in THF (90 mL) at 0 °C. After 30 min at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl (90 mL) and was extracted with Et_2O (3 × 75 mL). The combined organic layers were washed with 50 mL of water, 50 mL of saturated aqueous $NaHCO_3$, 50 mL of brine,

were dried over $MgSO_4$, and were evaporated to a yellow oil. Purification by flash chromatography (5% ethyl acetate in hexanes) afforded 1.87 g (62% over 3 steps) of **45** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.88 (dd, J = 17.6, 11.0 Hz, 1H), 5.17 (dd, J = 17.6, 1.6 Hz, 1H), 5.01 (dd, J = 11.0, 1.6 Hz, 1H), 1.49–1.56 (m, 2H), 1.24–1.32 (br m, 8H), 1.03 (s, 2H), 0.85–0.89 (m, 3H), 0.04 (s, 9H).

2-Hexylbuta-1,3-diene (46).[14] A suspension of **45** (1.87 g, 8.2 mmol) in 6.8 mL of acetic acid saturated with ammonium acetate was stirred at 60 °C for 20 min. The reaction mixture was poured into 100 mL of water, neutralized with saturated aqueous $NaHCO_3$, and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with 75 mL of water, 75 mL of brine, dried over $MgSO_4$, and evaporated to an oil. Purification by flash chromatography (100% hexanes) afforded 0.59 g (53% yield) of **46** as a colorless oil. Spectral data matched those reported in the literature. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.37 (dd, J = 17.6, 11.0 Hz, 1H), 5.23 (d, J = 17.6 Hz, 1H), 5.05 (d, J = 10.4 Hz, 1H), 5.00 (s, 1H), 4.98 (s, 1H), 2.20 (t, J = 7.1 Hz, 2H), 1.44–1.54 (m, 2H), 1.27–1.37 (m, 6H), 0.87–0.91 (m, 3H).

(3-Bromobut-3-enyloxy)(*tert*-butyl)dimethylsilane (48). To a solution of 3-bromo-3-buten-1-ol (**47**) (1.0 g, 6.6 mmol) in 15 mL of DMF was added imidazole (0.90 g, 13 mmol), *t*-butyldimethylsilyl chloride (1.5 g, 9.9 mmol), and dimethylaminopyridine (81 mg, 0.66 mmol). After 12 h at rt, 15 mL of water was added, and the solution was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 45 mL of saturated aqueous $NaHCO_3$, 45 mL of brine, dried over $MgSO_4$, and concentrated.

Purification by flash chromatography (2% ethyl acetate in hexanes) afforded 1.26 g (72% yield) of **48** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.63 (d, J = 1.1 Hz, 1H), 5.46 (d, J = 1.6 Hz, 1H), 3.79 (t, J = 6.3 Hz, 2H), 2.62 (t, J = 6.3 Hz, 2H), 0.89 (s, 9H), 0.07 (s, 6H).

***Tert*-butyldimethyl(3-methylenepent-4-enyloxy)silane (49).** Following the same procedure as **34**, **48** (1.0 g, 3.8 mmol), vinylmagnesium bromide (1.0 M in THF, 7.5 mL, 7.5 mmol), and $Pd(PPh_3)_4$ (218 mg, 0.19 mmol) in 20 mL benzene afforded 0.61 g (76% yield) of **49** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.36 (dd, J = 17.6, 11.3 Hz, 1H), 5.24 (d, J = 17.6 Hz, 1H), 5.06 (d, J = 11.0 Hz, 1H), 5.06 (broad s, 1H), 5.03 (broad s, 1H), 3.74 (t, J = 7.1Hz, 2H), 2.46 (t, J = 7.1 Hz, 2H), 0.90 (s, 9H) 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 143.4, 139.1, 117.6, 113.5, 62.6, 35.2, 26.1, 18.6, –5.0. HRMS (EI) calc. for $C_{12}H_{24}OSi$: 212.1597, found 212.1592.

2-Iodoprop-2-en-1-ol (51).[12] Following the same procedure as **33**, propargyl alcohol (3.1 mL, 3.0 g, 54 mmol), trimethylsilyl chloride (16 mL, 14 g, 130 mmol), sodium iodide (19.3 g, 128 mmol), and water (1.2 mL, 1.2 g, 6.4 mmol) in 110 mL of acetonitrile afforded 4.67 g (46% yield) of **51** as a purple oil (15% ethyl acetate in hexanes). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.39 (q, J = 1.6 Hz, 1H), 5.85–5.87 (m, 1H), 4.17 (t, J = 1.4 Hz, 2H), 2.09 (br s, 1H).

***Tert*-butyl(2-iodoallyloxy)dimethylsilane (52).**[20] To a solution of **51** (0.52 mL, 1.0 g, 5.4 mmol) in 40 mL of CH_2Cl_2 at 0 °C was added dimethylaminopyridine (0.66 g,

5.4 mmol) and *t*-butyldimethylsilyl chloride (0.90 g, 6.0 mmol). After 12 h at rt, the reaction mixture was diluted with 40 mL of water and was extracted with 2 × 40 mL of CH_2Cl_2. The combined organic layers were washed with 40 mL of brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography afforded 1.31 g (81% yield) of **52** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.42 (q, J = 1.6 Hz, 1H), 5.81 (q, J = 1.6 Hz, 1H), 4.18 (t, J = 1.6 Hz, 2H), 0.92 (s, 9H), 0.10 (s, 6H).

***Tert*-butyldimethyl(2-methylenebut-3-enyloxy)silane (53).** Following the same procedure as **34**, **52** (1.3 g, 4.4 mmol), vinylmagnesium bromide (1M in THF, 8.7 mL, 8.7 mmol), and $Pd(PPh_3)_4$ (252 mg, 0.22 mmol) in 23 mL benzene gave 0.24 g (28% yield) of **53** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.39 (dd, J = 17.9, 11.0 Hz, 1H), 5.33 (br s, 1H), 5.17 (d, J = 18.1 Hz, 1H), 5.11 (br s, 1H), 5.04 (d, J = 11.0 Hz, 1H), 4.35 (t, J = 1.5 Hz, 2H), 0.93 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 145.1, 136.8, 114.9, 113.2, 62.6, 26.1, 18.6, –5.2. HRMS (EI) calc. for $C_{11}H_{22}OSi$: 198.1440, found 198.1449.

General Procedure for Cross-metathesis Reactions Using 2-Substituted 1,3-Butadienes (Table 3.3). Entry 1, (*E*)-4-methylenedec-2-enyl acetate (54). To a solution of **2** (12 mg, 0.014 mmol) in benzene (1.5 mL) was added 1,4-diacetoxy-*cis*-2-butene (**6**) (100 mg, 0.58 mmol) and diene **46** (40 mg, 0.29 mmol). The solution stirred at 60 °C for 12h, and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (5% ethyl acetate:hexanes) to give 44 mg (72% yield, >20:1 E/Z) of **54** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.23 (d, J

= 16.0 Hz, 1H), 5.70 (dt, J = 15.7, 6.6 Hz, 1H), 4.96 (br s, 1H), 4.94 (br s, 1H), 4.55 (dd, J = 6.3, 1.1 Hz, 2H), 2.11 (t, J = 7.0 Hz, 2H), 2.01 (s, 3H), 1.36–1.43 (m, 2H), 1.18–1.27 (m, 6H), 0.80-0.84 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 171.0, 145.6, 136.8, 122.4, 116.7, 65.4, 32.0, 31.9, 29.4, 28.2, 22.8, 21.2, 14.3. HRMS (EI) calc. for $C_{13}H_{22}O_2$: 210.1620, found 210.1616.

Entry 2, (*E*)-4-methylenedec-2-enyl benzoate (59). Following the general procedure for **54**, diene **46** (40 mg, 0.29 mmol), 1,4-dibenzoyl-2-butene (**37**) (171 mg, 0.58 mmol), and **2** (12 mg, 0.014 mmol) in 1.4 mL benzene gave 57 mg (73% yield, >20:1 E/Z) of **59** as a colorless oil. The product was not separated from allyl benzoate formed in the reaction (1.0:0.46 **59**/allyl benzoate). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05–8.09 (m, 2H), 7.53–7.60 (m, 1H), 7.44 (t, J = 7.4 Hz, 2H), 6.40 (d, J = 15.7 Hz, 1H), 5.90 (dt, J = 15.9, 6.3 Hz, 1H), 5.06 (br s, 1H), 5.03 (br s, 1H), 4.88 (dd, J = 6.3, 1.1 Hz, 2H), 2.22 (t, J = 6.9 Hz, 2H), 1.45–1.58 (m, 2H), 1.27–1.36 (m, 6H), 0.86–0.91 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.6, 145.6, 136.8, 133.2, 133.1, 129.8, 128.5, 122.6, 116.7, 65.8, 32.1, 31.9, 29.4, 28.2, 22.8, 14.2. HRMS (EI) calc. for $C_{18}H_{24}O_2$: 272.1776, found 272.1778.

Entry 3, (*E*)-4,4,5,5-tetramethyl-2-(3-methylenenon-1-enyl)-1,3,2-dioxaborolane (60). Following a slight modification of the general procedure for **54**, vinyl boronate **25** (89 mg, 0.58 mmol), diene **46**, (40 mg, 0.29 mmol), and **2** (25 mg, 0.029 mmol) in 1.5 mL benzene for 2 h at 60 °C (followed by the same work-up) gave 56 mg (73% yield, >20:1 E/Z) of **60** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.03 (d, J = 18.4

Hz, 1H), 5.59 (d, J = 18.4 Hz, 1H), 5.16 (br s, 1H), 5.13 (br s, 1H), 2.20 (t, J = 7.4 Hz, 2H), 1.41–1.48 (m, 2H), 1.20–1.34 (m, 6H), 1.27 (s, 12H), 0.85–0.89 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 152.0, 147.6, 119.3, 83.4, 31.9, 31.5, 29.5, 28.5, 25.0, 22.9, 14.3. HRMS (EI) calc. for $C_{16}H_{29}BO_2$: 264.2261, found 264.2251.

Entry 4, (*E*)-6-(*tert*-butyldimethylsilyloxy)-4-methylenehex-2-enyl benzoate (61). Following the general procedure for **54**, diene **49** (40 mg, 0.19 mmol), 1,4-dibenzoyl-2-butene (**37**) (112 mg, 0.38 mmol), and **2** (8 mg, 0.009 mmol) in 1 mL benzene gave 46 mg (70% yield, >20:1 E/Z) of **61** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.05–8.10 (m, 2H), 7.53–7.59 (m, 1H), 7.41–7.47 (m, 2H), 6.39 (d, J = 15.9 Hz, 1H), 5.92 (dt, J = 15.9, 6.3 Hz, 1H), 5.12 (br s, 1H), 5.07 (br s, 1H), 4.88 (d, J = 6.3 Hz, 2H), 3.75 (t, J = 7.1 Hz, 2H), 2.47 (t, J = 7.1 Hz, 2H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 142.3, 136.6, 133.2, 130.4, 129.8, 128.5, 122.9, 118.6, 65.7, 62.4, 35.7, 26.1, 18.5, –5.1. HRMS (EI) calc. for $C_{20}H_{31}O_3Si$ [M+H]: 347.2043, found 347.2047.

Entry 5, (*E*)-9-(*tert*-butyldimethylsilyloxy)-7-methylenenon-5-enyl acetate (62). Following the procedure for **54**, diene **49** (40 mg, 0.19 mmol), 5-hexenyl acetate (**36**) (107 mg, 0.75 mmol), and **2** (8 mg, 0.009 mmol) in 1 mL benzene gave 46 mg (75% yield, >20:1 E/Z) of **62** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.05 (d, J = 15.7 Hz, 1H), 5.69 (dt, J = 15.9, 6.9 Hz, 1H), 4.94 (br s, 1H), 4.88 (br s, 1H), 4.06 (t, J = 6.6 Hz, 2H), 3.71 (t, J = 7.1 Hz, 2H), 2.43 (t, J = 6.9 Hz, 2H), 2.13 (q, J = 6.9 Hz, 2H), 2.04 (s, 3H), 1.58–1.68 (m, 2H), 1.41–1.51 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR

(75 MHz, $CDCl_3$, ppm): δ 171.4, 143.0, 132.7, 129.8, 115.3, 64.6, 62.8, 36.0, 32.5, 28.3, 26.2, 25.9, 21.2, 18.6, –5.1. HRMS (EI) calc. for $C_{18}H_{35}O_3Si$ [M+H]: 327.2356, found 327.2366.

Entry 6, (*E*)-*tert*-butyldimethyl(3-methylene-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-enyloxy)silane (63). Following a slight modification of the general procedure for **54**, diene **49** (40 mg, 0.19 mmol), vinyl boronate **25** (59 mg, 0.38 mmol), and **2** (16 mg, 0.019 mmol) in 1 mL benzene for 2 h at 60 °C (followed by the same work-up) gave 44 mg (69% yield, >20:1 E/Z) of **63** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.03 (d, J = 18.4 Hz, 1H), 5.60 (d, J = 18.4 Hz, 1H), 5.23 (br s, 1H), 5.18 (br s, 1H), 3.70 (t, J = 7.1 Hz, 2H), 2.46 (dt, J = 7.1, 1.1 Hz, 2H), 1.27 (s, 12H), 0.87 (s, 9H), 0.02 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 151.8, 144.1, 121.0, 83.4, 62.4, 35.0, 26.1, 25.0, 18.5, –5.1. HRMS (EI) calc. for $C_{18}H_{35}BO_3Si$: 338.2449, found 338.2455.

Entry 7, (*E*)-*tert*-butyldimethyl(2-methylene-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)but-3-enyloxy)silane (64). Following a slight modification of the general procedure for **54**, diene **53** (40 mg, 0.20 mmol), vinyl boronate **25** (62 mg, 0.40 mmol), and **2** (17 mg, 0.020) in 1 mL benzene for 2 h at 60 °C (followed by the same work-up) gave 37 mg (approximately 73% pure; ~40% yield based on impurities and unreacted, inseparable boronate **25**, >20:1 E/Z) of impure **64** as a yellow oil. Peaks given in spectral data are only those corresponding to **64**. ^{1}H NMR (300 MHz, $CDCl_3$,

ppm): δ 7.06 (d, J = 18.9 Hz, 1H), 5.49 (q, J = 1.9 Hz, 1H), 5.48 (d, J = 18.7 Hz, 1H), 5.28 (br s, 1H), 4.36 (t, J = 1.6 Hz, 2H), 1.28 (s, 12H), 0.92 (s, 9H), 0.07 (s, 6H).

Entry 8, (*E*)-4-((*tert*-butyldimethylsilyloxy)methyl)penta-2,4-dienyl benzoate (65). Following the general procedure for **54**, diene **53** (40 mg, 0.20 mmol), 1,4-dibenzoyl-2-butene (**37**) (119 mg, 0.40), and **2** (9 mg, 0.01 mmol) in 1 mL benzene gave 42 mg (63% yield, >20:1 E/Z) of **65** as a pale yellow oil. Compound **65** was not separated from allyl benzoate formed in the reaction (1.0:0.55 **65**:allyl benzoate). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.03–8.09 (m, 2H), 7.53–7.59 (m, 1H), 7.44 (t, J = 8.0 Hz, 2H), 6.40 (d, J = 15.9 Hz, 1H), 5.87 (dt, J = 15.9, 6.3 Hz, 1H), 5.37 (br s, 1H), 5.17 (br s, 1H), 4.86 (d, J = 6.3 Hz, 2H), 4.35 (s, 2H), 0.92 (s, 9H), 0.09 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 166.5, 144.0, 134.0, 133.2, 129.8, 128.5, 122.7, 118.4, 116.1, 65.8, 62.9, 26.1, 18.5, –5.2. HRMS (EI) calc. for $C_{19}H_{29}O_3Si$ [M+H]: 333.1886, found 333.1888.

(*E*)-1-(3-methylpenta-1,3-dienyl)benzene (71). To a solution of **2** (14 mg, 0.016 mmol) in benzene (1.5 mL) was added vinylboronate **25** (50 mg, 0.32 mmol) and diene **28** (26 mg, 0.32 mmol), and the solution stirred at 40 °C for 2.5 h. The reaction solution was cooled to rt, and $Pd(PPh_3)_4$ (11 mg, 0.0097 mmol), bromobenzene (50 mg, 0.32 mmol), and NaOEt (2M in EtOH, 0.46 mL, 0.91 mmol) were added. The solution stirred at 80 °C for 5 h. The reaction mixture was purified by flash chromatography (100% hexanes) to give 23 mg (45% yield) of **71** as a colorless oil. A small amount (13%) of the cross product missing the terminal methyl group was identified by two broad singlets at 5.09 ppm and 5.14 ppm in the ^{1}H NMR spectrum (terminal C=CH_2). Characterization

data matched those in the literature.[21] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.41–7.48 (m, 2H, both *E*- and *Z*-isomers), 7.28–7.36 (m, 2H, both *E*- and *Z*-isomers), 7.18–7.26 (m, 1H, both *E*- and *Z*-isomers), 6.90 (d, J = 16.2 Hz, 1H, *Z*-isomer), 6.83 (d, J = 16.2 Hz, 1H, *E*-isomer), 6.57 (d, J = 15.9 Hz, 1H, *Z*-isomer), 6.46 (d, J = 15.9 Hz, 1H, *E*-isomer), 5.73 (q, J = 7.1 Hz, 1H, *E*-isomer), 5.56 (q, J = 7.1 Hz, 1H, *Z*-isomer), 1.95 (m, 3H, *Z*-isomer), 1.88 (t, J = 1.1 Hz, 3H, *E*-isomer), 1.82 (d, J = 7.1 Hz, 3H, *E*-isomer); terminal methyl resonance of *Z*-isomer overlaps with those of the major isomer.

References

[1] (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Chatterjee, A. K. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 2.8.

[2] There are a limited number of examples where trisubstituted olefins are formed in high yields; see (a) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939–1942. (b) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751–1753.

[3] Brummer, O.; Ruckert, A.; Blechert, S. *Chem. Eur. J.* **1997**, *3,* 441–446.

[4] Crowe, W. E.; Zhang, Z. J. *J. Am. Chem. Soc.* **1993**, *115*, 10998–10999.

[5] BouzBouz, S.; Cossy, J. *Org. Lett.* **2001**, *3*, 1451–1454.

[6] For other examples of chemoselective CM using NHC-containing ruthenium catalysts, see (a) Michaelis, S.; Blechert, S. *Org. Lett.* **2005**, *7*, 5513–5516. (b) Lautens, M.; Maddess, M. L. *Org. Lett.* **2004**, *6*, 1883–1886.

[7] (a) Wagner, J.; Martin Cabrejas, L. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255–9260. A similar

approach was taken in the synthesis of (–)-griseoviridin: (b) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem. Int. Ed.* **2000**, *39*, 1664–1666.

[8] Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903–10908.

[9] Recent reviews of enyne metathesis: (a) Mori, M. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Weinheim, Germany: 2003; Chapter 2.5. (b) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317–1382.

[10] Some of the work described in this chapter was published: Funk, T. W.; Efskind, J.; Grubbs, R. H. *Org. Lett.* **2005**, *7*, 187–190.

[11] Enyne CM often works better under an atmosphere of ethylene; see Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855–1858.

[12] Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675–676.

[13] Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483–486.

[14] Brown, P. A.; Bonnert, R. V.; Jenkins, P. R.; Lawrence, N. J.; Selim, M. R. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1893–1900.

[15] Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, *20*, 3845–3847.

[16] Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082–6083.

[17] See ref 1a and the introduction to chapter 2 of this dissertation.

[18] Louie, J.; Grubbs, R. H. *Organometallics* **2002**, *21*, 2153–2164.

[19] (a) ref. 9b. (b) Katritzky, A. R.; Nair, S. K.; Khokhlova, T.; Akhmedov, N. G. *J. Org. Chem.* **2003**, *68*, 5724–5727. (c) Lee, H.-Y.; Kim, H. Y.; Tae, H.; Kim, B. G.; Lee, J.

Org. *Lett*. **2003**, *5*, 3439–3442. (d) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett*. **2001**, *42*, 171–174.

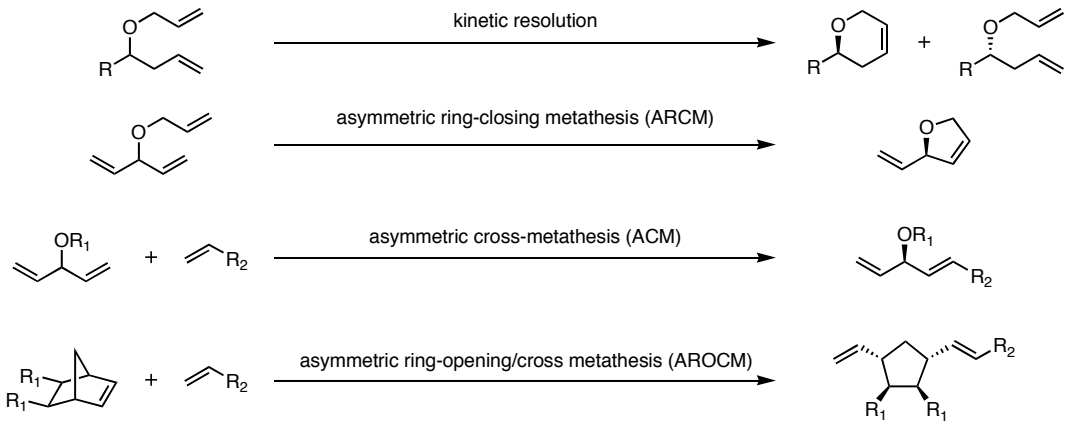
[20] Lai, M. T.; Li, D.; Oh, E.; Liu, H. W. *J. Am. Chem. Soc*. **1993**, *115*, 1619–1628.

[21] Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc*. **2001**, *123*, 6989-7000.

Chapter 4
Asymmetric Ring-Closing Metathesis with Ruthenium Alkylidenes Bearing Chiral, Monodentate *N*-Heterocyclic Carbene Ligands

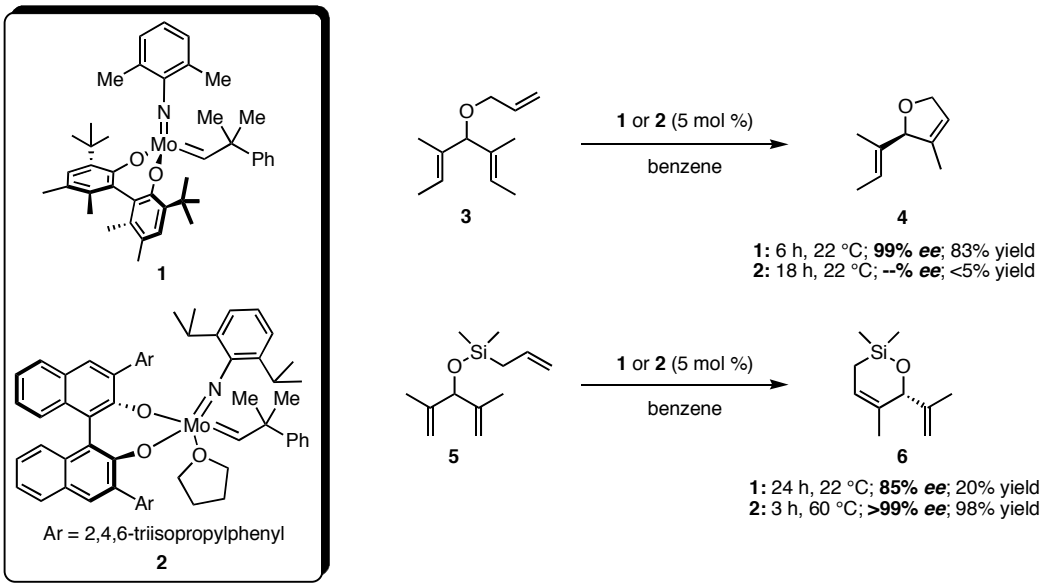
Introduction

Asymmetric olefin metathesis does not seem possible at first glance, because no sp^3-hybridized carbons are formed during a metathesis reaction. Instead of creating a new sp^3 carbon, asymmetric metathesis reactions form chiral compounds through either kinetic resolutions of racemates or desymmetrizations of achiral or meso compounds (Scheme 4.1). When chiral metathesis catalysts are used, enantioenriched products can be generated.[1] The kinetic resolutions ideally involve selective ring closing of one enantiomer of a chiral diene while leaving the other enantiomer untouched. Asymmetric ring-closing metathesis (ARCM) and asymmetric cross-metathesis (ACM) are intramolecular and intermolecular reactions that produce a chiral center through desymmetrizations of trienes or dienes, respectively. Asymmetric ring-opening/cross metathesis (AROCM) reactions create multiple chiral centers by desymmetrizing meso compounds.



Scheme 4.1. Examples of asymmetric olefin metathesis reactions.

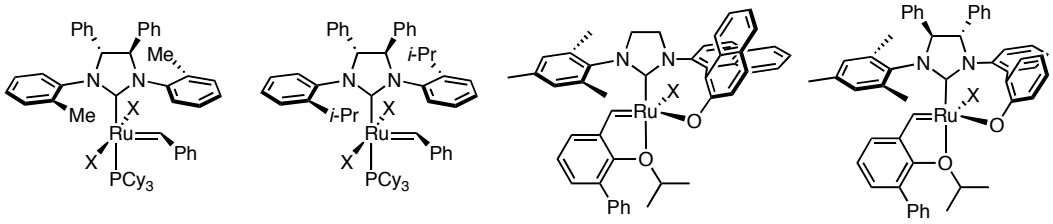
Most asymmetric olefin metathesis reactions have been catalyzed by chiral molybdenum complexes, including kinetic resolutions, ARCM, AROCM, and asymmetric ring-opening/ring-closing metathesis (ARORCM).[1] No single chiral molybdenum alkylidene catalyst is efficient and selective in every asymmetric metathesis reaction. Therefore, the Schrock and Hoveyda groups have generated a library of catalysts and screened them to find the best one for a given transformation. For example, complex **1** catalyzes the formation of 5-membered ring **4** with high enantioselectivity and yield, but it is inefficient and less selective in generating the six-membered ring **6** (Scheme 4.2).[2] On the other hand, catalyst **2** affords **6** in 98% yield and in >99% *ee*, but is almost completely inactive in the synthesis of **4**.[3] More than 30 chiral molybdenum complexes have been made by varying the imido, alkylidene, and bidentate phenoxide groups.[1b]



Scheme 4.2. Differences in selectivity and efficiency between chiral molybdenum catalysts.

Much like the parent achiral molybdenum catalysts, the chiral complexes are more sensitive to air, moisture, and a variety of common functional groups than most

ruthenium olefin metathesis catalysts and need to be handled and stored in an inert atmosphere.[1b] Molybdenum olefin metathesis catalysts are incompatible with carboxylic acids, ketones, aldehydes, most alcohols, and primary amines. Because the ruthenium catalysts are so tolerant and therefore user friendly, enantioselective variants would also be expected to find widespread use. Unfortunately, only a few examples of ruthenium-catalyzed asymmetric olefin metathesis exist. Two classes of chiral ruthenium metathesis catalyst have been explored (Figure 4.1): those containing monodentate *N*-heterocyclic carbenes (NHCs) with chirality in the backbone developed in the Grubbs group (**7** and **8**)[4] and those containing chiral, bidentate NHC/binaphthyl ligands developed in the Hoveyda group (**9** and **10**).[5] Complexes **9** and **10** catalyze AROCM in up to 98% *ee*,[6] but they exhibit reduced reactivity and selectivity toward ARCM relative to catalysts **7** and **8**.[7]

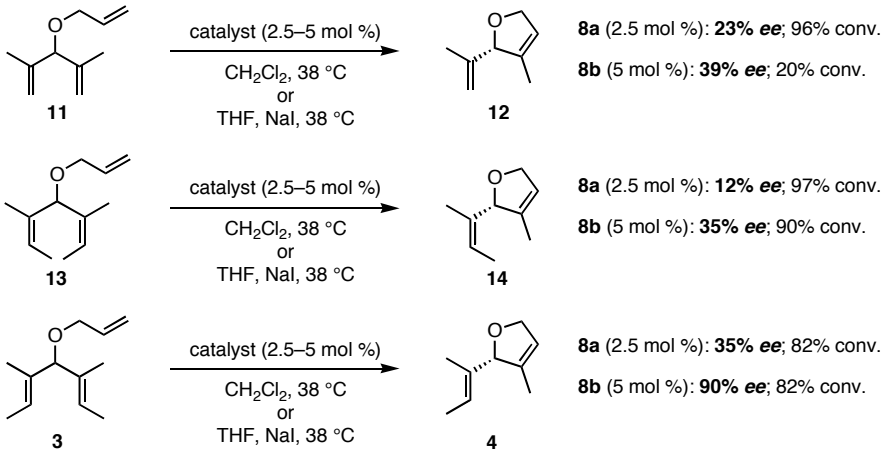


7a (X = Cl) **8a** (X = Cl) **9a** (X = Cl) **10a** (X = Cl)
7b (X = I) **8b** (X = I) **9b** (X = I) **10b** (X = I)

Figure 4.1. Representative examples of chiral ruthenium olefin metathesis catalysts.

The initial study of ruthenium metathesis catalysts bearing chiral, monodentate NHCs involved screening six catalysts and three substrates.[4] Complexes with NHCs derived from 1,2-diaminocyclohexane exhibited low enantioselectivities (0%–13% *ee*), but those derived from 1,2-diphenylethylenediamine catalyzed the formation of a 2,5-dihydrofuran in up to 90% *ee*. Catalyst **8b** was the most selective catalyst, and the three substrates it was reacted with are shown in Scheme 4.3. The enantioselectivity of the reaction is highly dependent on the olefin substitution and the type of halide on the

catalyst, with iodide typically affording the highest *ee*. These were the only substrates explored in this study.



Scheme 4.3. ARCM of three trienes catalyzed by chiral ruthenium benzylidene complexes.

After the initial examination of catalysts **8a** and **8b** in ARCM, the focus shifted toward catalyzing AROCM and ACM with catalysts **8a** and **8b**.[8] Moderate enantioselectivities (12%–82%) were observed over a wide range of substrates for both AROCM and ACM. Based on the results from the initial report,[4] it was clear that the 1,2-diphenylethylenediamine-based catalysts were superior to those derived from 1,2-diaminocyclohexane. Additionally, increasing the size of the ortho substituent from methyl to isopropyl (**7b** to **8b**) improved the enantioselectivity of the formation of **4** (85% *ee* with **7b** and 90% *ee* with **8b**). Therefore, new catalysts containing varying substitution around the *N*-bound aryl rings that were based on **8** were targeted in this study. These substituted catalysts were tested in AROCM and ACM,[8] but the results presented in this chapter are focused on ARCM with ruthenium catalysts that have substitution in the meta positions of the *N*-bound aryl rings. Very few substrates were tested in the initial study (Scheme 4.3), so one of the goals of the research presented here was to explore the substrate scope of this family of meta-substituted catalysts. Based on

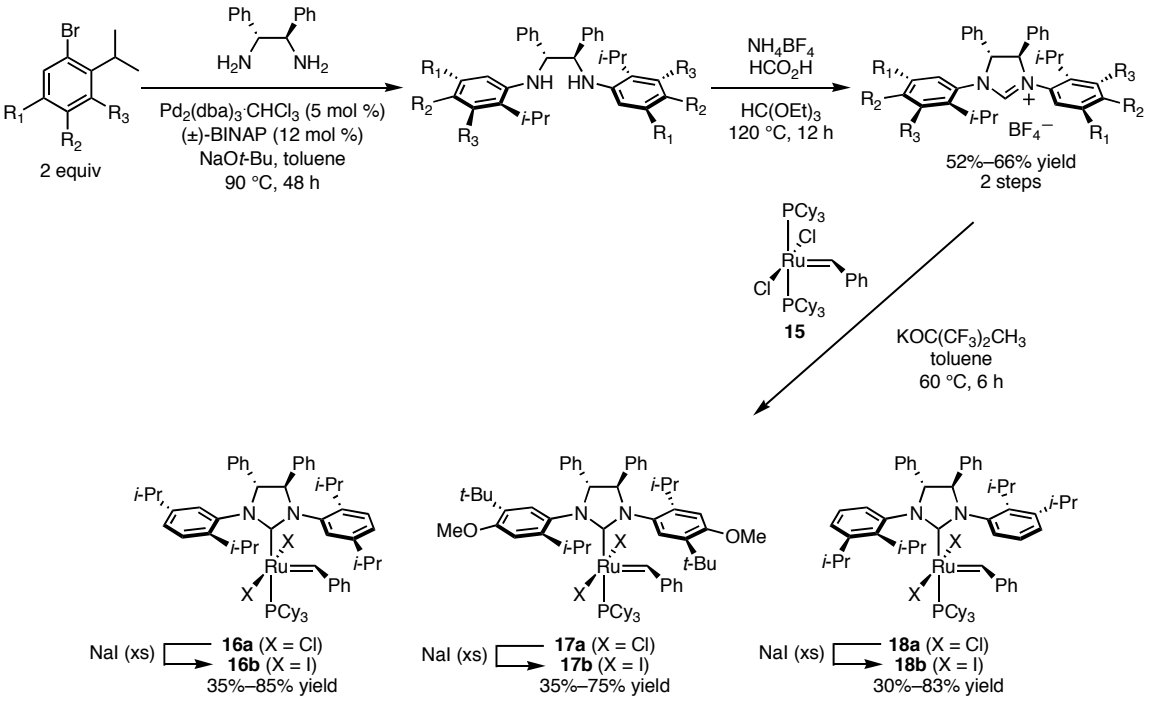
the success of **8** in ARCM, it was expected that these new variants would also be selective and efficient.

Results and Discussion[9]

Design and Synthesis of Chiral Ruthenium Catalysts. One of the reasons the *N*-bound aryl rings were modified is that it was relatively straightforward to introduce structural changes to them, and therefore many different catalysts could be made. Initially, catalysts with ortho substituents larger than isopropyl were the targeted complexes. Attempts to increase the size of the ortho substituent to *t*-butyl were unsuccessful. Although a catalyst with an ortho cyclohexyl group was made, enantiomeric excesses were low (18% *ee* for the formation of **4**), and the catalyst was unstable. It was thought that the para position was too remote from the ruthenium center, and changes there would not have any effect on the enantioselectivities. Therefore, catalysts with substitution in the meta position of the *N*-bound aryl rings were made.

A modular synthesis was used to access the desired chiral, non-racemic NHCs. Most of this work was done by Jacob Berlin, another graduate student in the group, and all of the experimental details (including the synthesis of the aryl bromides) have been published.[9] Briefly, these complexes were all generated by the same strategy (Scheme 4.4). Two equivalents of an aryl bromide were coupled to commercially available (1*R*,2*R*)-1,2-diphenylethylenediamine using a $Pd_2(dba)_3$/(±)-BINAP catalyst system,[10] and the resulting chiral diamines were reacted with triethylorthoformate and NH_4BF_4 to afford dihydroimidazolium BF_4^- salts. These carbene precursors were then reacted with bis-phosphine complex **15** and potassium hexafluoro-*t*-butoxide to generate the desired chiral

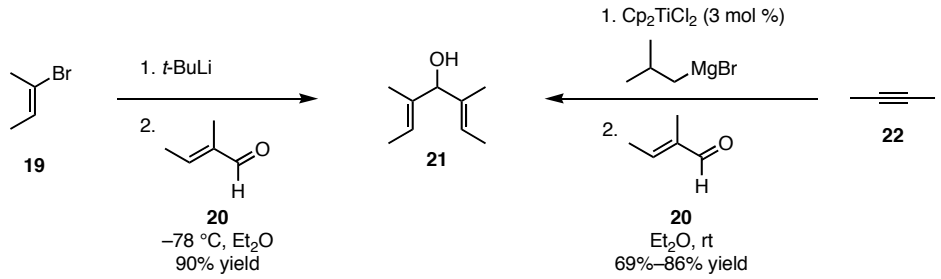
olefin metathesis catalysts as dichlorides. The yields for the last step varied due to a challenging chromatographic purification of the complexes. The para methoxy group in complexes **17a** and **17b** was used as a synthetic handle during the aryl bromide synthesis and was not expected to effect the enantioselectivities. The dichloride complexes (**16a**–**18a**) were all stable to air and moisture for at least 6 months in the solid state, and the diiodide variants (**16b**–**18b**) were generated in situ by the addition of 25 equivalents of sodium iodide to the analogous dichloride catalyst. They were never isolated.



Scheme 4.4. Synthesis of chiral ruthenium olefin metathesis catalysts.

Substrate Synthesis. Only three substrates were used in the initial study of ruthenium catalysts bearing chiral, monodentate NHCs.[4] It was discovered that one triene (**3**) underwent ARCM in 90% *ee*, but no other compounds similar to **3** were tested. One of the major goals of the research presented here was to explore the substrate scope of this family of catalysts, so the first trienes that were made were derivatives of **3**. The building

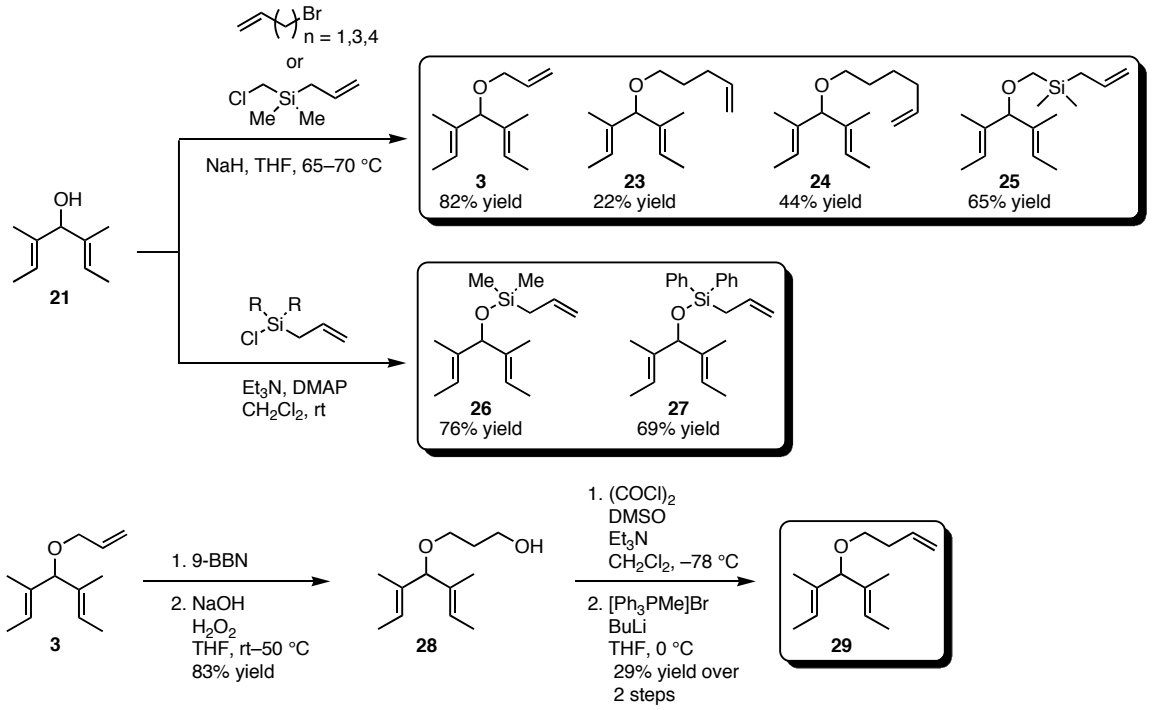
block for all of these substrates was alcohol **21**, and early on in this work **21** was made from vinyl bromide **19** (Scheme 4.5). Compound **19** was commercially available, and **21** was obtained in high yield. As more substrates were made, larger quantities of **21** were needed. Unfortunately, vinyl bromide **19** was expensive (>$2000/mol), and so an alternative route to **21** was developed. When 2-butyne (**22**) ($295/mol) was treated with isobutylmagnesium bromide in the presence of a catalytic amount of titanocene dichloride, a vinyl Grignard reagent was generated in situ.[11] Tiglic aldehyde (**20**) was added to the solution, and **21** was generated. Multigram quantities of alcohol **21** were made using this procedure.



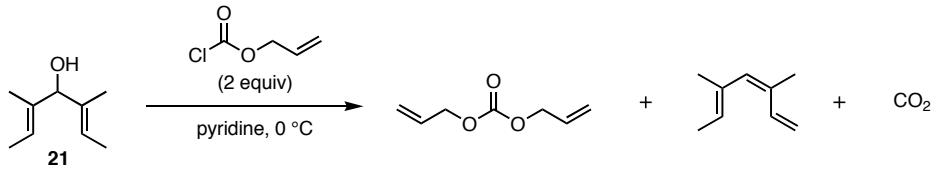
Scheme 4.5. Two approaches to the synthesis of alcohol **21**.

With alcohol **21** in hand, many different substrates were prepared (Scheme 4.6). Most of the alkyl ethers were made by simply generating the sodium alkoxide of **21**, and reacting it with an electrophile. The low yields obtained in the synthesis of **23** and **24** were attributed to steric hindrance around the hydroxyl group in **21**. Attempts to make **29** by alkylating **21** with 4-bromo-1-butene or 4-iodo-1-butene were completely unsuccessful. When the sodium alkoxide was used, elimination to form 1,3-butadiene occurred instead of the desired nucleophilic displacement. The route that finally led to **29** involved a chemoselective hydroboration with 9-BBN followed by oxidation of the alkyl borane to primary alcohol **28**. The alcohol was oxidized to an aldehyde that was not

stable, so the crude material was subjected to a Wittig olefination to afford **29** in 29% yield over two steps. Silyl ethers **26** and **27** were both made using standard conditions. When electron-withdrawing groups such as allylchloroformate and vinylacetyl chloride were used as electrophiles, elimination of the carbonate or vinylacetate, respectively, occurred (Scheme 4.7).



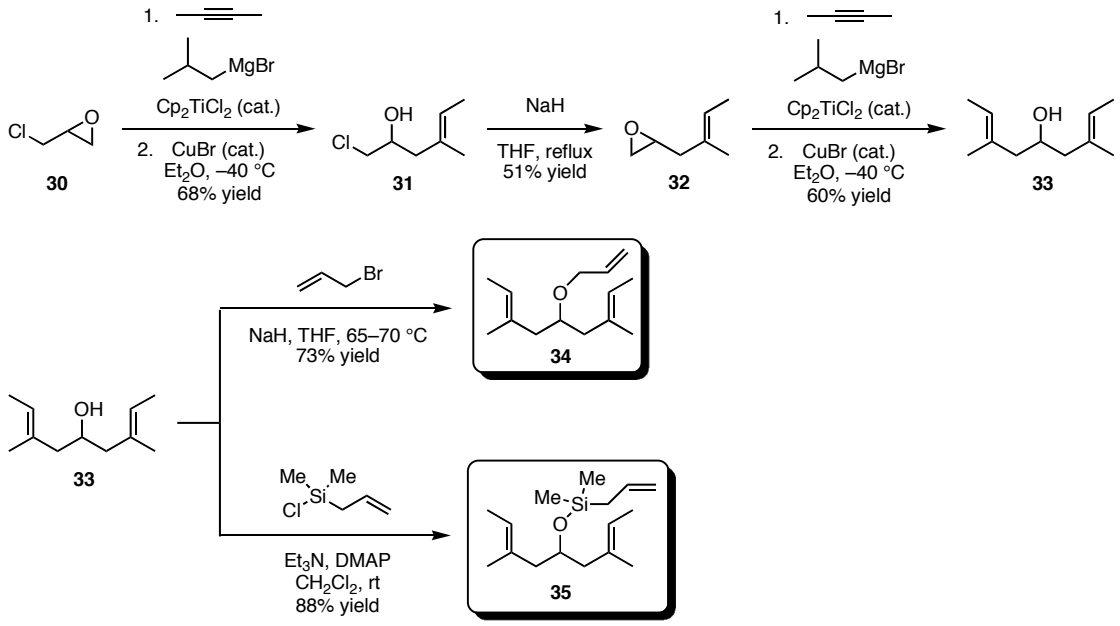
Scheme 4.6. Synthesis of ARCM substrates based on alcohol **21**.



Scheme 4.7. Elimination of a carbonate derivative of **21**.

In addition to substrates based on allylic alcohol **21**, trienes derived from homoallylic alcohol **33** were also made (Scheme 4.8). Compound **33** was synthesized in three steps from epichlorohydrin (**30**): the appropriate vinyl magnesium bromide was generated in situ,[11] and in the presence of catalytic CuBr, it opened the epoxide. An

intramolecular nucleophilic displacement reaction transformed chlorohydrin **31** into epoxide **32**, which underwent a second epoxide-opening process to afford **33**. The allyl ether **34** and the dimethylallylsilyl ether **35** were formed using standard conditions, and they are analogous to compounds **3** and **26**, respectively.

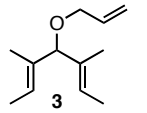
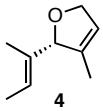
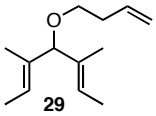
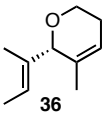
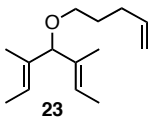
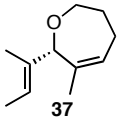
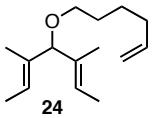
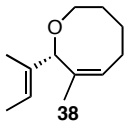


Scheme 4.8. Synthesis of ARCM substrates based on alcohol **33**.

Efficiency and Enantioselectivity of Chiral Ruthenium Catalysts. All of the achiral trienes were treated with catalysts **8**, **16**, **17**, and **18** in the absence and presence of sodium iodide. The results of the ARCM reactions of the alkyl ethers derived from **21** are shown in Table 4.1. First, the addition of sodium iodide to the reaction had an enormous impact on the enantioselectivity, regardless of what substrate or catalyst was used. The enantiomeric excesses of the cyclic products increased up to 57% relative to those with the dichloride catalysts when the diiodide catalysts were used, and they were all >80%. Of the dichloride catalysts, **18a** was the most selective for all of the substrates in Table 4.1. As the meta substituent para to the isopropyl group increased in size

(catalysts **8a**, **16a**, and **17a**), the enantiomeric excess of the product decreased, but never by more than 17% when going from H to *t*-butyl. With the diiodide catalysts, this trend did not continue, and the selectivities were similar for **8b**, **16b**, and **17b**.

Table 4.1. ARCM of achiral, alkenyl ethers using chiral ruthenium olefin metathesis catalysts.

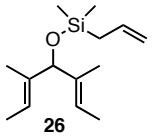
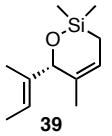
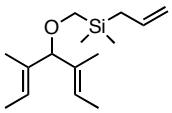
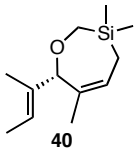
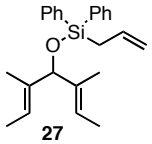
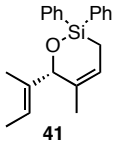
Substrate	Product	8	16	17	18
 **3**	 **4**	**35% *ee***, >98% conv NaI: **90% *ee***, >98% conv	**31% *ee***, >98% conv NaI: **84% *ee***, >98% conv	**30% *ee***, >98% conv NaI: **87% *ee***, >98% conv	**46% *ee***, >98% conv NaI: **90% *ee***, >98% conv
 **29**	 **36**	**68% *ee***, >98% conv NaI: **90% *ee***, >98% conv	**67% *ee***, >98% conv NaI: **88% *ee***, >98% conv	**64% *ee***, >98% conv NaI: **82% *ee***, 43% conv	**74% *ee***, >98% conv NaI: **84% *ee***, 70% conv
 **23**	 **37**	**65% *ee***, >98% conv NaI: **85% *ee***, 5% conv	**56% *ee***, >98% conv NaI: **87% *ee***, 51% conv	**48% *ee***, 91% conv NaI: **85% *ee***, 70% conv	**76% *ee***, 93% conv NaI: **83% *ee***, 20% conv
 **24**	 **38**	**65% *ee***, ~1% conv NaI: **85% *ee***, ~2% conv	**57% *ee***, 4% conv NaI: **88% *ee***, 5% conv	**51% *ee***, 9% conv NaI: 0% conv	**71% *ee***, ~2% conv NaI: 0% conv

Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h.

Conversions >90% were obtained in all of the reactions with the dichloride catalysts, except when **24** was used. The product of the RCM of **24** is an eight-membered ring containing a trisubstituted alkene (**38**), and these types of products are typically challenging to access using RCM.[12] Even though the loadings of the diiodide catalysts were doubled relative to the dichloride catalysts, lower conversions were often observed. This may be due to catalyst decomposition, as diiodide ruthenium metathesis catalysts are typically less stable than the corresponding dichloride catalyst.[13] Reactions with dichloride catalysts were performed in CH_2Cl_2 and reactions with diiodide catalysts were in THF, so the conversions may also be dependent on solvent.

The trienes derived from **21** bearing silyl alkenyl ethers were also treated with catalysts **8**, **16**, **17**, and **18**, and the results are shown in Table 4.2. For all of the substrates, the enantiomeric excess were ≥75% with the dichloride catalysts. The diiodide catalysts were typically more selective, but the differences were not nearly as large as with the substrates in Table 4.1. Additionally, as in Table 4.1, selectivity decreased as steric bulk in the meta position increased (**8a**, **16a**, and **17a**), but there was no simple trend with the analogous diiodide catalysts.

Table 4.2. ARCM of achiral, silyl alkenyl ethers using chiral ruthenium olefin metathesis catalysts.

Substrate	Product	8	16	17	18
 **26**	 **39**	**83% *ee***, >98% conv NaI: **86% *ee***, 68% conv	**81% *ee***, >98% conv NaI: **90% *ee***, >98% conv	**75% *ee***, >98% conv NaI: **85% *ee***, >98% conv	**92% *ee***, >98% conv NaI: **92% *ee***, 58% conv
 **25**	 **40**	**84% *ee***, 88% conv NaI: **87% *ee***, 15% conv	**80% *ee***, 91% conv NaI: **90% *ee***, 75% conv	**78% *ee***, 90% conv NaI: **86% *ee***, 50% conv	**92% *ee***, 93% conv NaI: **92% *ee***, 10% conv
 **27**	 **41**	**77% *ee***, >98% conv NaI: **83% *ee***, 96% conv	N/D	N/D	**80% *ee***, >98% conv NaI: N/D

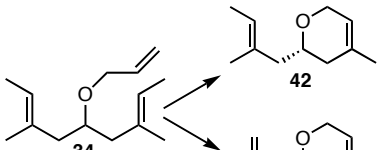
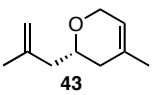
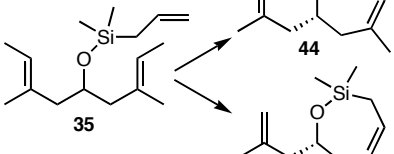
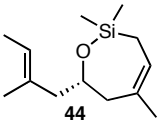
Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. N/D = not determined.

The most exciting discovery was that **18a** catalyzed the ARCM of **26** and **25** in 92% *ee*. Not only was this the highest enantiomeric excess obtained using this family of catalysts, but also it was achieved without the need for sodium iodide. Moreover, since the dichloride catalysts are generally more stable than the diiodide catalysts, lower catalyst loadings could be used. No difference in enantioselectivity and a decrease in conversion was observed when **18b** was reacted with **26** and **25**. It was thought that the success of these substrates was due in part to the methyl groups on the dimethylsilyl

linker increasing the difference in energies of the diastereomeric transition states, so a triene with two phenyl groups (**27**) was made. Unfortunately, the enantioselectivity of the reactions with **27** were lower than with **26** and **25**.

In addition to the substrates based on allylic alcohol **21**, the trienes derived from **33** were also reacted with **8**, **16**, **17**, and **18** (Table 4.3). When both **34** and **35** underwent ARCM, small amounts of the products lacking a terminal methyl group (**43** and **45**) were formed. The enantiomeric excesses of the methylated and demethylated products were generally similar, suggesting the methyl group was removed after the ring closing occurred. The matched or mismatched interaction of the catalysts with the chiral products could explain the increase or decrease in enantiomeric excess of the demethylated products relative to the methylated products observed in some cases (compare **44** and **45** with catalyst **16b**). The reactions with allyl ether **34** went to complete conversion with all of the catalysts, but the reactions were only moderately selective (up to 58% *ee*). Greater enantioselectivities were obtained with silyl ether **35**, but reactions with the analogous substrates based on alcohol **21** (Table 4.2) were more selective under these conditions.

Table 4.3. ARCM of substrates derived from alcohol **33**.

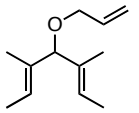
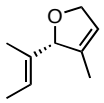
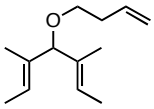
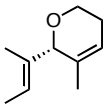
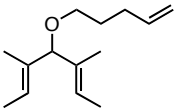
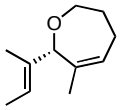
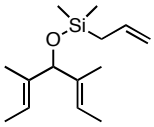
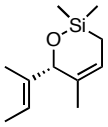
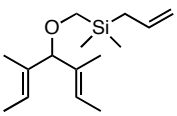
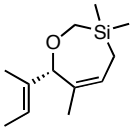
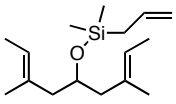
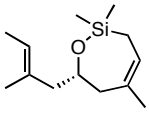
Substrate	Product	8	16	17	18
	**42**	**31%ee**, >95% conv NaI: **35%ee**, >95% conv	**37%ee**, >95% conv NaI: **58%ee**, >95% conv	**23%ee**, >95% conv NaI: **44%ee**, >95% conv	**31%ee**, >95% conv NaI: N/D
34	 **43**	**29%ee**, <5% conv NaI: **38%ee**, <5% conv	**35%ee**, <5% conv NaI: **54%ee**, <5% conv	**28%ee**, <5% conv NaI: **47%ee**, <5% conv	**13%ee**, >95% conv NaI: N/D
	 **44**	**56%ee**, 91% conv NaI: **78%ee**, >95% conv	**39%ee**, 80% conv NaI: **74%ee**, 92% conv	**36%ee**, 95% conv NaI: **51%ee**, 89% conv	**52%ee**, >98% conv NaI: **77%ee**, >98% conv
35	**45**	**32%ee**, 9% conv NaI: **61%ee**, <5% conv	**27%ee**, 20% conv NaI: **35%ee**, 8 conv	**30%ee**, 5% conv NaI: **22%ee**, 11% conv	**6%ee**, <2% conv NaI: not observed

Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. N/D = not determined.

The data in Tables 4.1 and 4.2 showed that the addition of meta substituents para to the ortho isopropyl group (catalysts **16** and **17**) only caused minor fluctuations in the enantioselectivity of the reaction. The introduction of a meta isopropyl group ortho to the ortho isopropyl group (**18**) increased the selectivity of the catalyst. From these reactions it became clear that the parent complex **8b**, and the diisopropyl variant **18a**, were the most selective catalysts of those tested. Therefore, isolated yields were obtained from ARCM reactions between **8b** or **18a** and selected achiral trienes (Table 4.4). The yields for **4** and **36** were moderately reduced due to the volatility of the products during purification. Attempts to use less than 4 mol % of **8b** resulted in incomplete conversion of **3** to **4**. When a more challenging substrate (**23**) was used, **8b** formed the product in 85% *ee*, but in only 5% conversion. Catalyst **18a** is much more efficient (presumably because it is more stable that **8b**),[13] and **37** was isolated in 92% yield and 76% *ee*.[14]

Compound **39** was isolated in 77% yield using almost 1 g of **26** with less than 1 mol % of **18a**, and no decrease in enantiomeric excess occurred relative to the screening reactions.

Table 4.4. ARCM reactions of selected achiral trienes with chiral ruthenium catalysts.

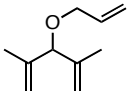
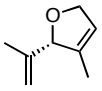
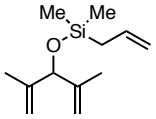
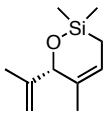
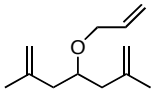
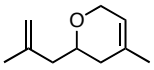
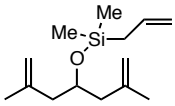
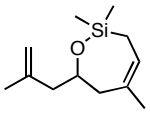
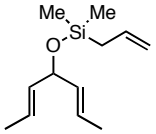
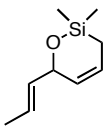
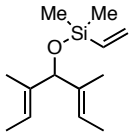
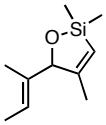
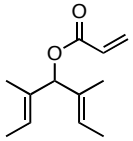
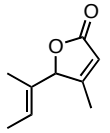
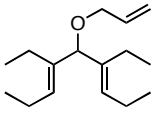
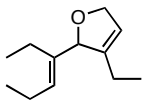
Triene	Product	Catalyst (mol %)	*ee* (%)[a]	Conv. (%)[b]	Yield (%)
 **3**	 **4**	**8b** (4)	90	>98	64
 **29**	 **36**	**8b** (4)	90	>98	77
 **23**	 **37**	**8b** (4)	85	5	N/D
		18a (2)	76	93	92[c]
 **26**	 **39**	**18a** (0.8)	92	>98	77[d]
 **25**	 **40**	**18a** (1)	92	65	64
 **35**	 **44**	**8b** (4)	78	>98	98

Conditions for reactions with **8b**: NaI (25 equiv relative to catalyst) and **8a** in THF (0.055 M in triene) for 1 h at rt, then add triene and stir for 2 h at 40 °C; conditions for reactions with **18a**: triene, CH_2Cl_2 (0.055 M in triene), and **18a** for 2 h at 40 °C. [a] Enantiomeric excesses determined by chiral GC. [b] Determined by ^{1}H NMR spectrum of crude reaction mixture. [c] See reference 14. [d] Reaction done on a 4 mmol (0.95 g) of **26** scale. N/D = not determined.

All of the achiral trienes described above have two trisubstituted olefins with cis methyl groups. These substrates were used because, in the initial study with catalyst **8**, compounds with no terminal methyl groups (**11**, Scheme 4.3) or with trans methyl groups (**13**, Scheme 4.3) underwent ARCM with low enantioselectivity. Many other substrates

were screened with the chiral ruthenium metathesis catalysts to determine if the substrate scope was general or limited, and the best results are shown in Table 4.5.

Table 4.5. Best results of ARCM reactions with "other" achiral trienes.

Triene	Product	Catalyst (mol %)	*ee* (%)	Conv. (%)
 **11**	 **12**	**17a** (2)	39	>98
		16b (4)	64	9
 **5**	 **6**	**17a** (2)	50	93
 **46**	 **43**	**17a** (2)	26	>98
		16b (4)	61	9
 **47**	 **45**	**18a** (2)	–8	>98[a]
		16b (4)	15	18
 **48**	 **49**	**50** (5)	N/A	>98 complex mixture
 **51**	 **52**	**50** (5)	N/A	18%
 **53**	 **54**	**50** (5)	N/A	>98% complex mixture
 **55**	 **56**	**8b** (4)	29	>98

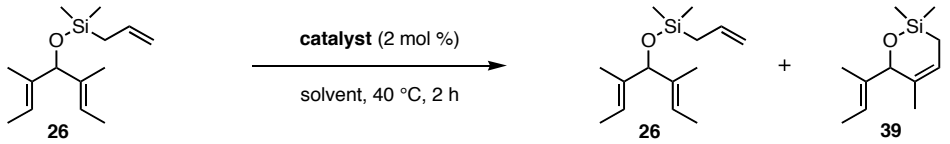
Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. [a] See appendix 1 for information on an interesting side product. Catalyst **50** = $(H_2IMes)RuCl_2(=CHPh)$. N/A = not applicable.

The meta substituted catalysts (**16** and **17**) were more selective than **8** in reactions with **11**, but **12** was formed in either poor *ee* and excellent conversion or moderate *ee* and poor conversion. Compound **5**, which is analogous to the excellent substrate **26**, was only formed in 50% *ee*. Just as in the reactions with substrates **11** and **5**, trienes **46** and **47** did not undergo ARCM as selectively and efficiently as the analogous compounds with cis methyl groups.[15] The lower conversions obtained using diiodide catalysts with **11**, **46**, and **47** may be due to the formation of a ruthenium methylidene instead of an ethylidene that would be generated with **3**, **34**, and **35**. Ruthenium methylidenes are known to decompose more rapidly than other alkylidenes, and in these cases decomposition may have occurred more quickly than the cross-metathesis reaction that introduced the triene to the catalyst.[16]

Substrates other than those lacking terminal methyl groups were also explored. The RCM of **48** with the achiral catalyst **50** ($(H_2IMes)RuCl_2(=CHPh)$) afforded a mixture of volatile products, but no starting material remained; secondary metathesis with the acyclic olefin in **49** likely occurred. Vinylsilanes typically cause decomposition of ruthenium metathesis catalysts,[17] so it was not surprising that very low yields of **52** were obtained when **51** was reacted with **50**. Acrylate **53** reacted with catalyst **50**, but a mixture of unidentified products were formed. Finally, because only trienes with cis methyl groups underwent ARCM in high enantioselectivities, substrate **55** was made to test if groups larger than methyl would work. The product (**56**) was formed in only 29% *ee*. It was clear from these data that chiral catalysts **8**, **16**, **17**, and **18** were only highly selective with a small set of substrates.

The conditions used in the ARCM reactions discussed above were very similar to the optimized conditions used in the initial report,[4] so various factors were reexamined to attempt to improve yields and enantiomeric excesses. A solvent screen was performed first (Table 4.6). Reactions performed in acetone, *N*,*N*-dimethylformamide (DMF), and acetonitrile afforded the product in <10% yield. Ethyl acetate and MTBE were better solvents, but the yields were still low. The best solvents were methylene chloride, benzene, and THF, where **39** was formed in >98%. The enantioselectivity was not affected when THF was used in place of CH_2Cl_2, and the slight reduction in benzene suggests that solvent coordination to the catalyst is not as important as in the molybdenum systems.[18]

Table 4.6. Solvent screen.



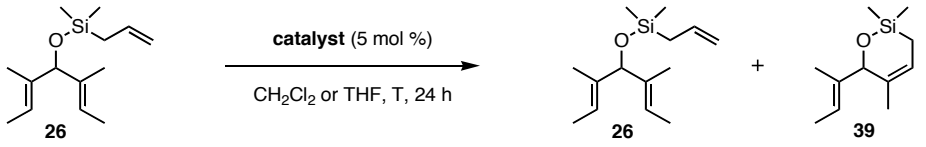
Solvent	Catalyst (mol %)	26 (%)	39 (%)	*ee* (%)
acetone	**50**	>90	<10	N/A
DMF	**50**	>90	<10	N/A
acetonitrile	**50**	>90	<10	N/A
t-butyl methyl ether	**50**	77	23	N/A
ethyl acetate	**50**	67	33	N/A
Et_2O	**50**	9	91	N/A
CH_2Cl_2	**18a**	<2	>98	92
benzene	**18a**	<2	>98	88
THF	**18a**	<2	>98	92

N/A = not applicable.

Another variable that was adjusted was the reaction temperature; it was lowered to 0 °C, and the conversions and enantioselectivities of the ARCM of **26** were explored (Table 4.7). When catalysts **8a** and **8b** were used, the enantioselectivities increased relative to the reactions at 40 °C. On the other hand, the enantioselectivities decreased

when ARCM reactions with **16b** and **18a** were done. The highest conversion of **26** at 0 °C was 40%, and in all cases the reactions were allowed to proceed for 24 h with 5 mol % of catalyst. It was suspected that catalyst initiation (phosphine dissociation) was slow at 0 °C, so acid was added in an attempt to increase the rate of initiation.[19] Unfortunately, no **39** was formed upon addition of either 1 equivalent of HCl in diethyl ether or 20 equivalents of benzoic acid relative to the catalyst. Although in some reactions a small increase in enantioselectivity was observed, this approach was not practical because the conversions were low.

Table 4.7. ARCM reactions at 0 °C.

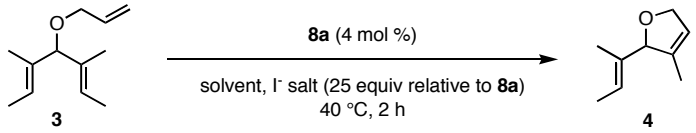


Catalyst (mol %)	Reaction at 0 °C		Reaction at 40 °C	
	ee (%)	Conv. (%)	*ee* (%)	Conv. (%)
8a	88	39	83	>98
8b	90	40	86	68
16b	88	29	90	>98
18a	87	25	92	>98

The last variable that was explored was a combination of the iodide source and the solvent in reactions with diiodide catalysts. The original protocol called for sodium iodide in THF,[4] but reactions with the dichloride catalysts were done in CH_2Cl_2, so sodium iodide and tetrabutylammonium iodide were tested in THF and CH_2Cl_2 (Table 4.8). By far the most selective combination is sodium iodide in THF. When sodium iodide in CH_2Cl_2 is used in place of THF, the enantioselectivity suffers drastically, although it is not as low as the reaction with just **8a** and no sodium iodide (35% *ee*). This could be due to the insolubility of sodium iodide in CH_2Cl_2. After 1 h in THF, the

sodium iodide/**8a** mixture dissolved completely (by visual inspection), but a white solid remained in CH_2Cl_2. The enantioselectivity also decreased when the iodide source was changed to tetrabutylammonium iodide, but it remained higher than the reaction without any iodide. The $[Bu_4N]I$ never completely dissolved in THF, but it appeared to be completely soluble in CH_2Cl_2. In both reactions **4** was formed in 59% *ee*. One explanation for the success of the NaI/THF combination is that NaI is soluble in THF but NaCl is not; so the equilibrium between I-bound and Cl-bound ruthenium is forced to generate only the ruthenium diiodide catalyst.

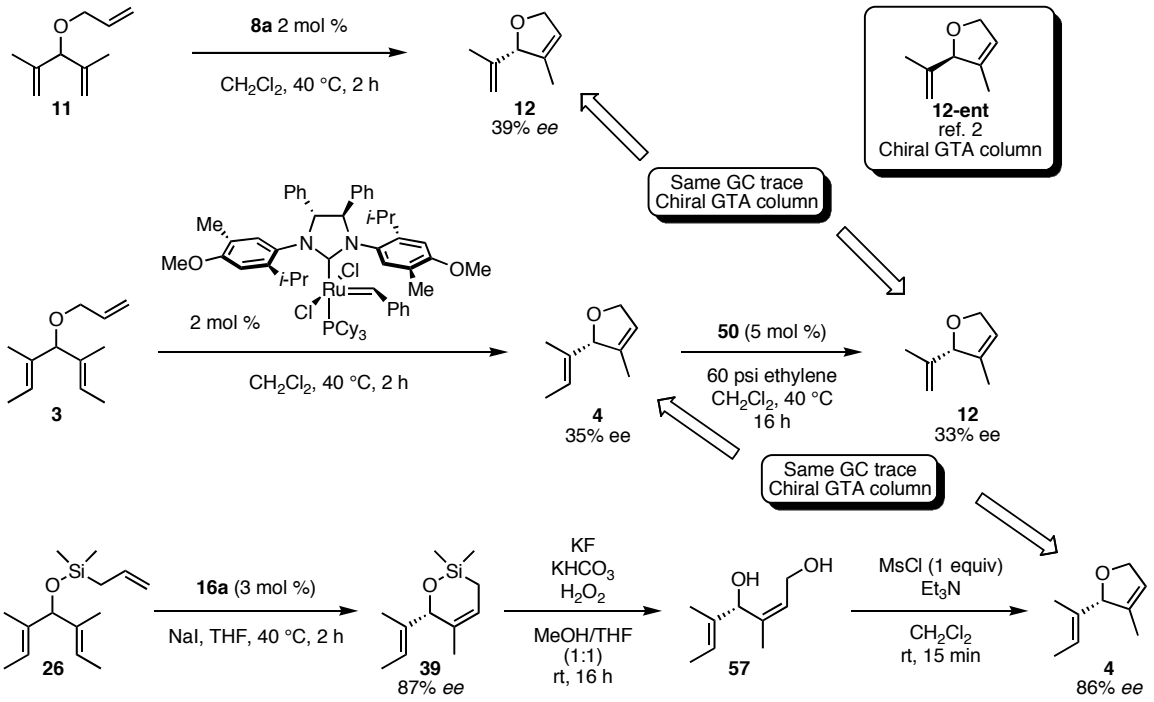
Table 4.8. Effects of iodide source and solvent in ARCM.



Iodide Salt	Solvent	*ee* (%)	Conv. (%)
none	CH_2Cl_2	35	>98
NaI	THF	90	>98
NaI	CH_2Cl_2	46	>98
$[Bu_4N]I$	THF	59	>98
$[Bu_4N]I$	CH_2Cl_2	59	>98

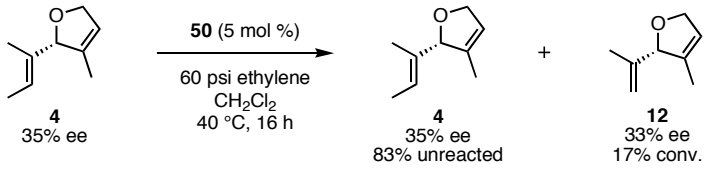
Absolute Stereochemistry Proof. All four chiral ruthenium catalysts tested in this study (**8**, **16**, **17**, and **18**) afforded the same enantiomer of the product for any given substrate in Tables 4.1–4.4, and the absolute stereochemistry of a few of the products was determined (Scheme 4.9). The absolute stereochemistry of **12-ent** was proven by an independent synthesis using a Sharpless kinetic resolution.[2] Compound **12-ent** was also made with chiral molybdenum catalysts, and a GC trace using a Chiraldex GTA column was used to determine the enantioselectivities of the reactions. The chiral ruthenium complex **8a** catalyzed the formation of **12**, which was also separated on a Chiraldex GTA column.

The GC traces showed that chiral catalyst **8a**, and therefore all the catalysts used in this study, afforded **12** in the absolute configuration shown in Scheme 4.9 and Table 4.5. The absolute configuration of **4** was determined by exposing it to ethenolysis conditions, which generated the same enantiomer of **12** that was obtained by the ARCM reaction of **11**. Finally, compound **39** was oxidized to diol **57** and exposed to a one-pot mesylation/intramolecular nucleophilic displacement sequence to afford the same enantiomer of **4** that was obtained by the ARCM of **3**. Chiral, cyclic products derived from a triene lacking terminal methyl groups (**11**), containing cis methyl groups and an alkenyl ether (**3**), and containing cis methyl groups and a dimethylsilyl alkenyl ether (**26**) all had the same absolute stereochemistry, which suggests that all of the products synthesized with **8**, **16**, **17**, or **18** have the same absolute configurations.



Scheme 4.9. Absolute stereochemistry proof.

Model to Rationalize Enantioselectivity of Chiral Ruthenium Catalysts. An understanding of how and why catalysts **8**, **16**, **17**, and **18** induce asymmetry in the RCM of achiral trienes would allow for the rational design of new, more selective catalysts. Therefore, a model to explain the experimental observations was developed. First, it was suspected that the ARCM reactions were irreversible, so enantioenriched **39** was treated with achiral catalyst **50** under the same conditions used in the ARCM reactions. No erosion in the enantiomeric excess of **39** was detected. Additional support for the irreversibility of ARCM came from the fact that essentially no loss in enantiomeric excess was observed when **4** was reacted with ethylene and achiral catalyst **50** under forcing conditions (Scheme 4.10).

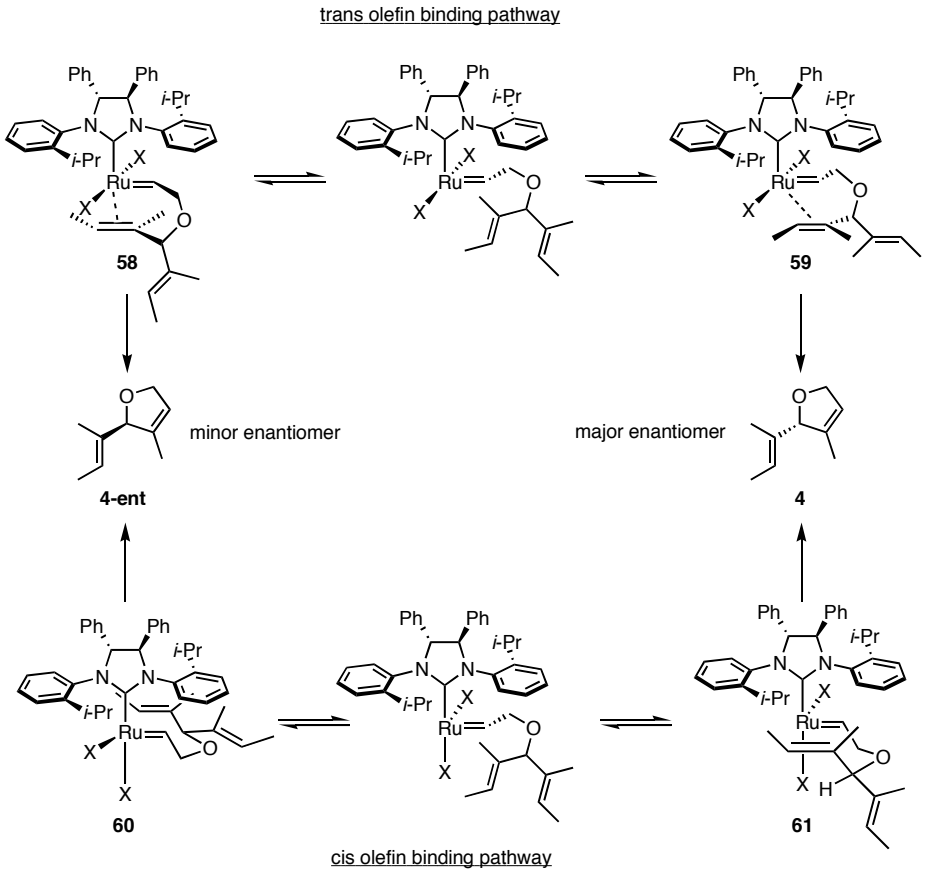


Scheme 4.10. Ethenolysis of **4**.

Chapters 2 and 3 of this dissertation describe how the achiral variant (**50**) of the chiral catalysts used here does not readily react with 1,1-disubstituted and trisubstituted alkenes. Therefore, all of the ARCM reactions are thought to proceed through a ruthenium alkylidene derived from the monosubstituted olefin present in every substrate. This species binds one of the diastereotopic alkenes and, through a metallacyclobutane intermediate/transition state, forms the ring-closed product.

Olefin coordination to the ruthenium is an important, stereodefining step; unfortunately, the actual position where the olefin binds relative to the NHC is unclear. There is experimental evidence to support coordination both cis and trans to the NHC.[20] If coordination is cis, than the alkene should bind to the catalyst face opposite the

isopropyl group to avoid an interaction with it (Scheme 4.11, **61**).[4] Either olefin could coordinate cis to the NHC, but structure **61** has the non-binding alkene in the more stable, pseudoequatorial position of the cyclic intermediate. Additionally, a hydrogen instead of a vinyl group is directed toward a halide. Completion of the ARCM reaction from **61** affords the major enantiomer.



Scheme 4.11. Proposed pathways leading to the desired product.

Recent experimental reports suggest the alkene may be coordinating trans to the NHC,[20b,c] and computational studies also support trans binding.[21] One computational study explored the energetics of **8b** reacting with **3**, and the most favored pathway is depicted in Scheme 4.11 (trans olefin binding pathway).[21a] The steric interaction that favors **59** over **58** is between the substituents on the alkylidene and the *N*-bound aryl ring.

The calculations concluded that the aryl ring is not orthogonal to the plane of the NHC (90°), but is instead tilted 75°. X-ray crystallographic analysis of a derivative of **7a** provided experimental evidence to support the calculations.[4] In this model, the side of the aryl ring with an isopropyl group was found to be smaller than the side with no substitution, so the larger alkylidene substituent (the ether) was positioned under the isopropyl group (Figure 4.2). Just as in **61**, the non-coordinating vinyl group is in the pseudoequatorial position in **59**.

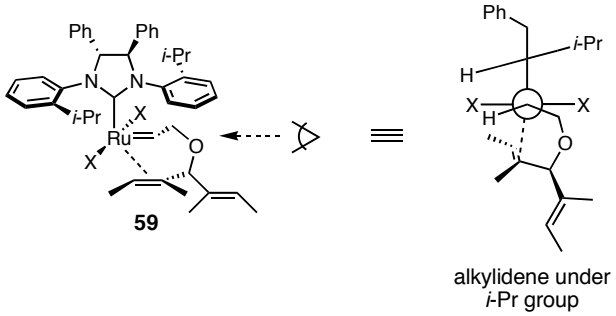


Figure 4.2. Suggested alkylidene position in trans olefin binding pathway.

Although the discussion presented here focuses on a substrate that forms a five-membered ring, the ideas could be extended to trienes that form other ring sizes. For a given substrate, there is presumably an energetically favored ring conformation that occurs once the olefin is coordinated to the ruthenium center. By adding substitution to the ring, the difference in energies of the cyclic, olefin-bound intermediates/transition states may increase, and the reaction may be more selective. That is a possible explanation as to why the reactions with the dimethylsilyl-containing trienes were more enantioselective than the reactions with substrates containing only alkyl ethers.

In almost every reaction shown in Tables 4.1–4.3, the addition of sodium iodide increased the enantioselectivity. One explanation for this effect is based on steric interactions: in the cis olefin binding pathway of Scheme 4.11, either a hydrogen (as

shown in **61**) or a vinyl group could be directed at the halide trans to the NHC. If the vinyl group was directed at the halide, the minor enantiomer would be formed. As the size of the halide is increased from chloride to iodide, the strength of the interaction between the two groups is be expected to increase, and the structure with a hydrogen in that position is expected to be lower in energy. In the trans olefin binding pathway, calculations suggest that as the halides increase in size, they are pushed away from each other and toward the alkylidene. That would put them in closer proximity to the reacting olefin, creating a smaller binding pocket, and therefore a more selective reaction.[21a]

Another explanation for the large iodide effect is based on electronic factors. It is known that phosphine dissociation occurs more quickly for the diiodide variant of achiral catalyst **50** than for **50**-dichloride, but the reactivities of the active species are similar.[13b] Phosphine dissociation is the rate-limiting step in catalyst initiation, so the fact that **50**-diiodide initiates quickly but does not increase the rate of product formation suggests that the active species derived from **50**-diiodide is less active than that derived from **50**-dichloride. Based on these data, it is reasonable to assume that the active species of the chiral diiodide catalysts are less active than the dichloride active species. When a highly active catalyst with an alkylidene derived from one of the achiral trienes discussed above is used, the rate- and enantio-determining step might be olefin binding. Therefore, metathesis would occur regardless of which diastereotopic alkene initially coordinated to the ruthenium center. On the other hand, a less-active catalyst may coordinate the olefin but not perform the ring-closing reaction. Instead, the olefin could dissociate and re-bind, setting up a rapid equilibrium. In this case ruthenacyclobutane formation, not olefin binding, would be the rate- and enantio-determining step, regardless of which conformer

is more stable. A change in the rate-determining step would also change the $\Delta\Delta G^{\ddagger}$, thereby affording a different distribution of enantiomeric products relative to the reactions catalyzed by a more active alkylidene.[22,23]

Two models have been proposed to explain the origin of enantioselectivity in reactions with the chiral ruthenium catalysts used in this study: one assuming the olefin coordinates cis to the NHC, and one assuming it coordinates trans to the NHC. At this point, neither of these pathways can be ruled out because no experiments that provide solid insight into catalyst structure during turnover have been developed. Both a steric and an electronic justification have been presented to explain why the diiodide catalysts are more selective than the dichloride catalysts. Unfortunately, no model has been developed that clarifies why the substrates containing trisubstituted alkenes with cis methyl groups afford products with much higher enantiomeric excesses.

Conclusion

Using novel, asymmetric, ruthenium metathesis catalysts containing chiral, monodentate NHCs, achiral trienes were desymmetrized in up to 92% *ee*. Catalysts **16** and **17**, which contained substitution para to an ortho isopropyl group, behaved very similarly to the parent chiral catalyst **8**. When the chloride ligands were exchanged for iodides, the enantioselectivities increased drastically in many reactions with all three catalysts. Complex **18** was the most selective catalyst, and it could be used in loadings of 1% or less to afford the desired products in up to 92% *ee* and in high conversions. Many achiral trienes with varying substitution were explored, and only those with two trisubstituted olefins with cis methyl groups afforded the desired products with high

enantioselectivities. Two proposed models that account for the observed products were presented, as well as two explanations as to why the diiodide catalysts are more selective than the dichloride catalysts. Although the substrate scope is limited and further development is needed to make these catalysts more general, the reactions are procedurally simple and very reliable due to the air and moisture stability of the ruthenium alkylidene catalysts.

Experimental

General Information. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a wavelength of 589 nm. The concentration "c" has units of g/100 mL (or 10 mg/mL) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain (10 g $KMnO_4$, 20 g Na_2CO_3, 1 L water) or UV light. Flash column chromatography was performed using silica gel 60 (230–400 mesh). All enantiomeric purities were determined by chiral GC (Chiraldex G-TA, 30 m × 0.25 mm or CP Chirasil-Dex-CB, 25 m × 0.25 mm) or chiral SFC (supercritical CO_2, ADH column, 214 nm UV detection) and were compared to racemic samples. All glassware was either oven dried or flame dried,

and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina. All commercial chemicals were used as obtained. Compounds **11**,[3] **12**,[3] **5**,[3] **6**,[3] **46**,[24] **43**,[24] **47**,[24] and **45**[24] are known compounds.

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (21).[11] Titanocene dichloride (444 mg, 1.78 mmol) was added to a solution of 2-butyne (**22**) (5.6 mL, 3.9 g, 71 mmol) and isobutylmagnesium bromide (2.0 M in diethyl ether, 33 mL, 66 mmol) in 60 mL Et_2O, and the solution stirred at rt for 1 h. *Trans*-2-methyl-2-butenal (**20**) (5.7 mL, 5.0 g, 59 mmol) in 30 mL Et_2O was added slowly, and the mixture stirred at rt for 3 h. It was quenched with saturated aqueous NH_4Cl (100 mL), filtered through a pad of Celite, and the organic layer was removed from the filtrate. The aqueous layer was extracted with ether (3 × 75 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to a brown oil. The oil was purified by flash chromatography (10% EtOAc in hexanes) to a yellow oil, which was distilled (Kugelrohr, 1 torr, 120 °C) to give 7.20 g (86% yield) of **21** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56 (qquint, J = 6.6, 1.4 Hz, 2H), 4.34 (s, 1H), 1.63 (dt, J = 6.9, 1.1 Hz, 6H), 1.47 (t, J = 1.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.1, 120.4, 81.8, 13.3, 12.1. HRMS (EI) *m/z* calc. for $C_9H_{16}O$: 140.1201, found 140.1203.

(2*E*,5*E*)-4-(Allyloxy)-3,5-dimethylhepta-2,5-diene (3). Alcohol **21** (200 mg, 1.43 mmol) was added dropwise to a suspension of NaH (60% in oil, 114 mg, 2.85 mmol) in 6 mL THF. After stirring at reflux for 15 min, the mixture was allowed to cool to rt, and

allyl bromide (430 mg, 3.57 mmol) was added. The mixture stirred at reflux for 4 h, was quenched with saturated aqueous NH_4Cl (10 mL), and was extracted with ether (3 × 15 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to an oil which was purified by flash chromatography (1% EtOAc in hexanes) to give 210 mg (82% yield) of **3** as a colorless oil. Spectral data matched those in the literature.[2] ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.85–5.98 (m, 1H), 5.55 (qq, J = 6.6, 1.1 Hz, 2H), 5.22–5.29 (m, 1H), 5.10–5.15 (m, 1H), 3.94 (br s, 1H), 3.85 (dq, J = 5.5, 0.8 Hz, 2H), 1.63 (dq, J = 6.6, 1.1 Hz, 6H), 1.46 (d, J = 1.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.6, 134.2, 121.2, 116.3, 88.3, 68.8, 13.3, 12.3. HRMS (EI) *m/z* calc. for $C_{12}H_{20}O$: 180.15142, found 180.15135.

(2*E*,5*E*)-3,5-Dimethyl-4-(pent-4-enyloxy)hepta-2,5-diene (23). **21** (400 mg, 2.9 mmol) was added slowly to a suspension of NaH (60% in oil, 140 mg, 3.4 mmol) in 5 mL THF at rt, and some bubbling occurred. After 2.5 h at rt, 5-bromo-1-pentene (0.68 mL, 5.7 mmol) was added, and the mixture was heated to reflux for 16 h. It was cooled to rt, carefully quenched with 20 mL water, and extracted with ether (3 × 25 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to an oil, which was purified by flash chromatography (1% EtOAc in hexanes, then 10% EtOAc in hexanes) to give 130 mg (22% yield) of **23** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.76–5.90 (m, 1H), 5.53 (qquint, J = 6.6, 1.4 Hz, 2H), 4.92–5.04 (m, 2H), 3.86 (s, 1H), 3.29 (t, J = 6.6 Hz, 2H), 2.13 (q, J = 6.9 Hz, 2H), 1.63–1.71 (m, 2H), 1.63 (d, J = 6.6 Hz, 6H), 1.46 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.9, 134.6,

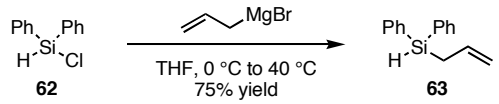
120.9, 114.6, 89.1, 67.5, 30.8, 29.4, 13.4, 12.3. HRMS (EI) *m/z* calc. for $C_{14}H_{24}O$: 208.1827, found 208.1828.

(2*E*,5*E*)-4-(Hex-5-enyloxy)-3,5-dimethylhepta-2,5-diene (24). **21** (500 mg, 3.6 mmol) was added slowly to a suspension of NaH (60% in oil, 285 mg, 7.1 mmol) in 7 mL THF at rt, and some bubbling occurred. After 15 min at rt, 6-bromo-1-hexene (0.96 mL, 7.1 mmol) was added, the mixture was heated to reflux for 16 h. It was cooled to rt, carefully quenched with 20 mL saturated aqueous NH_4Cl, and extracted with ether (3 × 25 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to an oil, which was purified by flash chromatography (2% EtOAc in hexanes) to give 346 mg (44% yield) of **24** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.74–5.88 (m, 1H), 5.53 (qt, J = 6.6, 1.1 Hz, 2H), 4.91–5.03 (m, 2H), 3.85 (s, 1H), 3.27 (t, J = 6.4 Hz, 2H), 2.06 (q, J = 7.1 Hz, 2H), 1.63 (d, J = 6.9 Hz, 6H), 1.54–1.60 (m, 2H), 1.40–1.52 (m, 2H), 1.45 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 139.2, 134.6, 120.9, 114.5, 89.1, 67.9, 33.9, 29.6, 25.9, 13.3, 12.3. HRMS (EI) *m/z* calc. for $C_{15}H_{26}O$: 222.1984, found 222.1971.

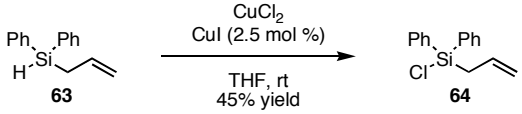
Allyl(((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)methyl)dimethylsilane (25). **21** (300 mg, 2.1 mmol) was added to a suspension of NaH (60% in oil, 103 mg, 2.6 mmol) in 3 mL THF and some bubbling occurred. After 30 min at rt, allylchloromethyldimethylsilane (0.70 mL, 0.63 g, 4.3 mmol) was added, and the mixture was heated to reflux for 16 h. The reaction mixture was cooled to rt, quenched with 20 mL water, and extracted with ether (3 × 20 mL). The organic layers were combined,

washed with brine, dried over $MgSO_4$, and evaporated to a yellow oil, which was purified by flash chromatography (100% hexanes) to give 349 mg (65% yield) of **25** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.81–5.95 (m, 1H), 5.51 (qquint, J = 6.6, 1.4 Hz, 2H), 4.98 (dq, J = 17.1, 1.7 Hz, 1H), 4.85–4.91 (m, 1H), 4.28 (s, 1H), 2.03–2.12 (m, 2H), 1.61 (dt, J = 6.9, 1.1 Hz, 6H), 1.43 (t, J = 1.1 Hz, 6H), 0.64–0.70 (m, 2H), 0.07 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 142.0, 136.5, 119.8, 112.8, 82.3, 27.6, 16.2, 13.3, 12.1, –1.4. HRMS (FAB) *m/z* calc. for $C_{15}H_{28}OSi$: 252.1910, found 252.1914.

Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)dimethylsilane (26). Allylchlorodimethylsilane (1.1 mL, 7.5 mmol) was added to a solution of **21** (1.0 g, 7.1 mmol), triethylamine (1.2 mL, 8.6 mmol), and *N*,*N*-dimethylaminopyridine (44 mg, 0.4 mmol) in 30 mL CH_2Cl_2 at rt. After 5 h the reaction was quenched with 50 mL water, the organic layer was removed, and the aqueous layer was extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to an oil. The oil was redissolved in hexanes and was filtered through a pad of neutral alumina. The filtrate was condensed to give 1.30 g (76% yield) of **26** as a colorless oil. Attempts to purify **26** by silica gel chromatography resulted in inconsistent yields and varying levels of purity due to product decomposition. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.70–5.85 (m, 1H), 5.52 (qquint, J = 6.9, 1.4 Hz, 2H), 4.80–4.90 (m, 2H), 4.30 (s, 1H), 1.61 (dt, J = 6.9, 1.1 Hz, 6H), 1.58–1.63 (m, 2H), 1.43 (t, J = 1.1 Hz, 6H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.4, 134.8, 119.9, 113.5, 82.4, 25.1, 13.3, 12.0, –1.9. HRMS (EI) *m/z* calc. for $C_{14}H_{26}OSi$: 238.1753, found 238.1752.



Allyldiphenylsilane (63).[25] To a solution of **62** (2.0 g, 1.8 mL, 9.1 mmol) in 9 mL of THF at 0 °C was added allylmagnesium bromide (1.0 M in diethyl ether, 9.7 mL, 9.7 mmol) over 5 min. After 10 min at 0 °C, the cloudy mixture was warmed to 40 °C. After 2 h at 40 °C, the reaction was quenched with a few pieces of ice followed by 30 mL saturated aqueous ammonium chloride. It was extracted with diethyl ether (3 × 30 mL), dried over $MgSO_4$, and concentrated to an oil. Purification by flash chromatography (100% pentane) afforded 1.53 g (75% yield) of **63** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.56–7.60 (m, 4H), 7.34–7.45 (m, 6H), 5.79–5.93 (m, 1H), 4.96 (dq, J = 17.1, 1.7 Hz, 1H), 4.88–4.93 (m, 1H), 4.87 (t, J = 3.6 Hz, 1H), 2.15 (dd, J = 7.7, 3.6 Hz, 2H).



Allylchlorodiphenylsilane (64).[26] A two-neck round-bottom flask topped with a Schlenk filter connected to another round-bottom flask was charged with anhydrous $CuCl_2$ (1.1 g, 8.0 mmol) and anhydrous CuI (19 mg, 0.10 mmol). After 2 pump/backfills with argon, the powders were suspended in 8 mL of THF, allyldiphenylsilane (**63**) (0.90 g, 4.0 mmol) was added, and the orange/brown slurry was stirred vigorously. After 16 h at rt, the reaction mixture was completely colorless and a white suspension was present. The round-bottom/Schlenk filter apparatus was inverted and placed under slight vacuum, and the filtrate was concentrated to a viscous oil. Purification by distillation (Kugelrohr, 0.4 torr, 210 °C) afforded 0.47 g (45% yield) of **64** as a pale yellow oil. ^{1}H NMR (300

MHz, $CDCl_3$, ppm): δ 7.63–7.67 (m, 4H), 7.38–7.50 (m, 6H), 5.75–5.90 (m, 1H), 5.00–5.05 (m, 1H), 4.97–5.00 (m, 1H), 2.36 (dt, J = 8.0, 1.4 Hz, 2H).

Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)diphenylsilane (27). To a solution of allylchlorodiphenylsilane (**64**) (370 mg, 1.43 mmol), triethylamine (0.28 mL, 2.0 mmol), and *N*,*N*-dimethylaminopyridine (8.7 mg, 0.07 mmol) in 7 mL CH_2Cl_2 was added **21** (241 mg, 1.72 mmol). After 5 h at rt, the reaction was poured into 20 mL of water, the organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to an oil. Purification by flash chromatography afforded 359 mg (69% yield) of **27** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.55–7.59 (m, 4H), 7.31–7.39 (m, 6H), 5.71–5.85 (m, 1H), 5.50 (tq, J = 6.9, 1.4 Hz, 2H), 4.81–4.91 (m, 2H), 4.39 (br s, 1H), 2.15 (dt, J = 8.0, 1.4 Hz, 2H), 1.56 (dt, J = 6.9, 0.8 Hz, 6H), 1.39 (t, J = 1.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.89, 135.32, 135.11, 133.62, 129.86, 127.74, 120.29, 114.97, 83.04, 22.48, 13.31, 11.94. HRMS (EI) *m*/*z* calc. for $C_{24}H_{30}SiO$ [M^+] 362.2066, found 362.2077.

(2*E*,5*E*)-4-(But-3-enyloxy)-3,5-dimethylhepta-2,5-diene (29). **3** (1.07 g, 5.90 mmol) in 3.6 mL THF was added to a solution of 9-BBN (0.5 M in THF, 14.2 mL, 7.12 mmol), and the solution stirred at rt. After 5 h 3.6 mL ethanol was added, followed by 1.4 mL aqueous 6 M NaOH and 2.8 mL 30% H_2O_2, and the reaction stirred at 50 °C for 1 h. It was diluted with 20 mL saturated aqueous $NaHCO_3$ and was extracted with ether (3 × 25 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4,

evaporated to an oil, and purified by flash chromatography (20% EtOAc in hexanes) to give 916 mg (83% yield) of **28** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.51 (qquint, J = 6.9 Hz, 1.1 Hz, 2H), 3.89 (br s, 1H), 3.79 (t, J = 5.2 Hz, 2H), 3.50 (t, J = 5.5 Hz, 2H), 2.62 (br s, 1H), 1.84 (quint, J = 5.8 Hz, 2H), 1.64 (dt, J = 6.6 Hz, 1.1 Hz, 6H), 1.46 (t, J = 1.4 Hz, 6H). DMSO (0.89 mL, 12.6 mmol) was added slowly to a solution of oxalyl chloride (0.66 mL, 7.56 mmol) in 15 mL CH_2Cl_2 at –78 °C. After 5 min a solution of **28** (500 mg, 2.52 mmol) in 5 mL CH_2Cl_2 was added to the –78 °C reaction solution, and it stirred for 30 min. Triethylamine (2.5 mL, 17.6 mmol) was added, and after 30 min at –78 °C, the reaction slowly warmed to rt. It was quenched with 40 mL water and extracted with ether (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to 448 mg of the crude aldehyde as an orange oil, which was used in the next step without further purification (attempts to purify this aldehyde by silica gel chromatography resulted in product decomposition and low (~30%) isolated yields). To a suspension of triphenylmethylphosphonium bromide (2.15 g, 6.0 mmol) in 20 mL THF at 0 °C was added *n*-butyllithium (2.5 M in hexanes, 2.0 mL, 5.0 mmol). After 20 min a solution of the crude aldehyde (448 mg, 2.3 mmol) in 5 mL THF was added slowly to the orange reaction mixture, and it stirred at 0 °C for 1 h. It was quenched with 30 mL saturated aqueous NH_4Cl and extracted with ether (3 × 25 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to an oil, which was purified by flash chromatography (1% EtOAc in hexanes) to give 179 mg of a colorless oil. To a solution of the oil in 10 mL CH_2Cl_2 was added 3% hydrogen peroxide, and the mixture was shaken for 15 minutes. The organic layer was removed, dried over Na_2SO_4, evaporated to an oil, and filtered through a plug of silica gel (1% EtOAc in

hexanes). The filtrate was concentrated to 145 mg (29% yield over 2 steps) of **29** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.77–5.92 (m, 1H), 5.53 (qquint, J = 6.9, 1.4 Hz, 2H), 4.98–5.11 (m, 2H), 3.88 (s, 1H), 3.33 (t, J = 6.9 Hz, 2H), 2.33 (q, J = 6.9 Hz, 2H), 1.63 (d, J = 6.6 Hz, 6H), 1.46 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.0, 134.5, 121.0, 116.2, 89.1, 67.6, 34.7, 13.3, 12.3. HRMS (EI) *m/z* calc. for $C_{13}H_{22}O$: 194.1671, found 194.1679.

(2*E*,7*E*)-3,7-Dimethylnona-2,7-dien-5-ol (33). Titanocene dichloride (212 mg, 0.85 mmol) was added to a solution of 2-butyne (2.4 mL, 30 mmol) and isobutylmagnesium bromide (2.0 M in diethyl ether, 15 mL, 30 mmol) in 30 mL Et_2O, and the solution stirred at rt for 1 h. This brown solution was slowly transferred via syringe to a suspension of CuBr (397 mg, 2.8 mmol) in Et_2O (75 mL) at –78 °C. After 5 min epichlorohydrin (**30**) (2.2 mL, 28 mmol) was added slowly to the mixture. It stirred at –78 °C for 3 h, and was allowed to warm to –40 °C where it continued stirring for 48 h. The reaction mixture was poured into 100 mL aqueous 1 N HCl and was extracted with ether (3 × 100 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to an oil, which was purified by flash chromatography (10% EtOAc in hexanes) to give 2.83 g (68% yield) of the chlorohydrin **31** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.36 (qq, J = 6.6, 1.1 Hz, 1H), 3.89–3.97 (m, 1H), 3.61 (dd, J = 11.0, 4.1 Hz , 1H), 3.50 (dd, J = 11.0, 6.3 Hz, 1H), 2.29 (dd, J = 13.5, 5.5 Hz, 1H), 2.20 (dd, J = 13.5, 8.0 Hz, 1H), 2.04 (br s, 1H), 1.66 (t, J = 1.1 Hz, 3H), 1.62 (dt, J = 6.9 Hz, 0.8 Hz, 3H). The chlorohydrin **31** (2.8 g, 19 mmol) was added slowly to a suspension of NaH (60% in oil, 1.13 g, 28 mmol) in 50 mL THF, and the mixture stirred at reflux for 16 h. It was cooled to rt,

quenched with saturated aqueous NH_4Cl until pH = 9 was reached, and was extracted with ether (3 × 50 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to a yellow oil, which was purified by flash chromatography (1% Et_2O in pentane) to give 1.08 g (51% yield) of the epoxide **32** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.34 (qq, J = 6.6, 1.1 Hz, 1H), 2.96–3.02 (m, 1H), 2.77 (dd, J = 4.9, 3.8 Hz, 1H), 2.49 (dd, J = 4.9, 2.7 Hz, 1H), 2.25 (dd, J = 14.8, 6.0 Hz, 1H), 2.16 (dd, J = 14.5, 5.5 Hz, 1H), 1.69 (t, J = 1.1 Hz, 3H), 1.61 (dq, J = 6.6, 1.1 Hz, 3H). Titanocene dichloride (69 mg, 0.28 mmol) was added to a solution of 2-butyne (0.8 mL, 10 mmol) and isobutylmagnesium bromide (2.0 M in diethyl ether, 4.9 mL, 10 mmol) in 10 mL Et_2O, and the solution stirred at rt for 1 h. This brown solution was slowly transferred via syringe to a suspension of CuBr (128 mg, 0.9 mmol) in Et_2O (25 mL) at –78 °C. After 5 min the epoxide **32** (1.0 g, 9 mmol) was added slowly to the mixture. It stirred at –78 °C for 2 h, and was allowed to warm to –40 °C where it continued stirring for 24 h. The reaction mixture was poured into 75 mL aqueous 1 N HCl and was extracted with ether (3 × 50 mL). The organic layers were combined, dried over Na_2SO_4, and evaporated to an oil, which was purified by flash chromatography (7% EtOAc in hexanes) to give 894 mg (60% yield, 21% over 3 steps) of **33** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.30 (q, J = 6.6 Hz, 2H), 3.75–3.82 (m, 1H), 2.01–2.15 (m, 4H), 1.79 (d, J = 1.7 Hz, 1H), 1.62 (s, 6H), 1.59 (d, J = 6.6 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 133.0, 122.2, 66.6, 47.7, 16.0, 13.7. HRMS (EI) *m/z* calc. for $C_{11}H_{20}O$: 168.1514, found 168.1515.

(2*E*,7*E*)-5-(Allyloxy)-3,7-dimethylnona-2,7-diene (34). Alcohol **33** (200 mg, 1.2 mmol) was added dropwise to a suspension of NaH (60% in oil, 95 mg, 2.4 mmol) in 5 mL THF. After stirring at reflux for 15 min, the mixture was allowed to cool to rt, and allyl bromide (360 mg, 3.0 mmol) was added. The mixture stirred at reflux for 12 h, was quenched with saturated aqueous NH_4Cl (30 mL), and was extracted with ether (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, and evaporated to an oil which was purified by flash chromatography (1.5% EtOAc in hexanes) to give 180 mg (73% yield) of **34** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.80–5.93 (m, 1H), 5.20–5.28 (m, 3H), 5.09–5.13 (m, 1H), 3.98 (dt, J = 5.4, 1.5 Hz, 2H), 3.50–3.58 (m, 1H), 2.18 (dd, J = 13.2, 6.9 Hz, 2H), 2.07 (dd, J = 13.5, 6.0 Hz, 2H), 1.62 (t, J = 1.2 Hz, 6H), 1.56–1.59 (m, 6H).

Allyl((2*E*,7*E*)-3,7-dimethylnona-2,7-dien-5-yloxy)dimethylsilane (35). To a solution of **33** (150 mg, 0.9 mmol), triethylamine (0.25 mL, 1.8 mmol), and *N*,*N*-dimethylaminopyridine (5 mg, 0.04 mmol) in 5 mL CH_2Cl_2 was added allylchlorodimethylsilane (0.20 mL, 1.3 mmol). After stirring at rt for 16 h, the reaction was quenched with 10 mL water and extracted with diethyl ether (3 × 20 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to an oil, which was purified by flash chromatography (1% EtOAc in hexanes) to give 209 mg (88% yield) of **35** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.70–5.84 (m, 1H), 5.23 (qq, J = 6.6, 1.4 Hz, 2H), 4.81–4.89 (m, 2H), 3.85 (quint, J = 6.3 Hz, 1H), 2.05–2.08 (m, 4H), 1.60 (t, J = 1.1 Hz, 6H), 1.58 (dt, J = 6.6, 0.8 Hz, 6H), 1.54–1.57 (m, 2H), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 134.7, 133.0, 121.7, 113.5, 70.5,

48.2, 25.4, 16.5, 13.6, –1.7. HRMS (EI) *m/z* calc. for $C_{16}H_{30}OSi$: 266.2066, found 266.2070.

General Procedure A: Asymmetric Ring-Closing Reactions with 8a, 16a, 17a, and 18a. Triene was added to a solution of dichloride catalyst (1–2 mol %) in CH_2Cl_2 (0.055 M), and the reaction stirred at 40 °C for 2 h. The solvent was evaporated, and the remaining residue was purified by flash chromatography to yield the desired cyclic diene.

General Procedure B: Asymmetric Ring-Closing Reactions with 8b, 16b, 17b, and 18b. A solution of NaI (25 equiv. relative to catalyst) and dichloride catalyst (4 mol %) in THF was stirred at rt for 1 h. Triene (0.055 M) was added, and the solution stirred at 40 °C for 2 h. The solvent was evaporated, and the remaining residue was purified by flash chromatography to yield the desired cyclic diene.

(*S*,*E*)-2-(But-2-en-2-yl)-3-methyl-2,5-dihydrofuran (4). Following general procedure B, **3** (40 mg, 0.22 mmol), **8a** (8.9 mg, 0.0089 mmol), and NaI (33 mg, 0.22 mmol) in 4 mL THF gave 19.8 mg (64% yield) of **4** as a pale yellow oil (5% Et_2O in pentane) in 90% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 60 min, retention times = 21.9 (major) and 23.4 (minor) min. $[\alpha]_D^{25}$ = +116.5 ($CHCl_3$, *c* = 0.55). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56 (quint, J = 1.6 Hz, 1H), 5.52 (q, J = 6.9 Hz, 1H), 4.88 (br s, 1H), 4.53–4.68 (m, 2H), 1.64 (dq, J = 6.9, 1.1 Hz, 3H), 1.56 (quint, J = 1.4 Hz, 3H), 1.47 (quint, J = 1.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 137.2, 135.6, 123.8, 121.5, 95.0, 75.6, 13.5, 12.4, 10.1. HRMS (EI) *m/z* calc. for $C_9H_{14}O$: 138.1045, found 138.1040.

(*S*,*E*)-6-(But-2-en-2-yl)-5-methyl-3,6-dihydro-2*H*-pyran (36). Following general procedure B, **29** (40 mg, 0.21 mmol), **8a** (8.2 mg, 0.0082 mmol), and NaI (31 mg, 0.21 mmol) in 3.8 mL THF gave 24.1 mg (77% yield) of **36** as a pale yellow oil (3% Et_2O in pentane) in 90% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 60 min, retention times = 30.6 (major) and 34.7 (minor) min. $[\alpha]_D^{26}$ = +43.0 ($CHCl_3$, *c* = 0.69). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.64–5.68 (m, 1H), 5.53 (q, J = 6.6 Hz, 1H), 4.29 (s, 1H), 3.88–3.94 (m, 1H), 3.53–3.61 (m, 1H), 2.19–2.32 (m, 1H), 1.85–1.96 (m, 1H), 1.64 (dd, J = 6.6, 1.1 Hz, 3H), 1.54 (t, J = 1.4 Hz, 3H), 1.47 (q, J = 1.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 134.9, 134.5, 125.2, 121.5, 84.1, 62.9, 25.8, 19.7, 13.5, 11.5. HRMS (EI) *m*/*z* calc. for $C_{10}H_{16}O$: 152.1201, found 152.1204.

(*S*,*Z*)-7-((*E*)-But-2-en-2-yl)-6-methyl-2,3,4,7-tetrahydrooxepine (37). Following a modified version of general procedure A, **23** (40 mg, 0.19 mmol) was added to a solution of **18a** (2.1 mg, 0.0019 mmol) in 3.5 mL CH_2Cl_2, and the reaction stirred at 40 °C. After 2 h, an additional portion of **18a** (2.1 mg, 0.0019 mmol) was added, and the solution stirred at 40 °C for an additional 2 h. The solvent was removed by evaporation, and the residue was purified by flash chromatography (4% EtOAc in hexanes) to give 29.4 mg (92% yield) of **37** as a yellow oil in 76% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 90 min, retention times = 75.1 (minor) and 76.6 (major) min. $[\alpha]_D^{24}$ = +164.0 ($CHCl_3$, *c* = 0.90). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.57–5.62 (m, 1H), 5.51 (q, J = 6.6 Hz, 1H), 4.26 (s, 1H), 3.85–3.92 (m, 1H), 3.57–3.66 (m, 1H), 2.48–2.59 (m, 1H), 1.87–2.03 (m, 2H), 1.67–1.80 (m, 1H), 1.67 (t, J = 2.2 Hz, 3H), 1.65 (d, J = 6.6 Hz, 3H), 1.50 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 137.2, 134.6, 125.3, 124.0, 91.4, 66.3, 29.2, 23.4, 21.9, 13.5, 12.5. HRMS (EI) *m/z* calc. for $C_{11}H_{18}O$: 166.1358, found 166.1353.

(*S*,*Z*)-8-((*E*)-But-2-en-2-yl)-7-methyl-3,4,5,8-tetrahydro-2*H*-oxocine (38). Following general procedure B, **24** (14 mg, 0.061 mmol), **16a** (3 mg, 0.003 mmol), and NaI (9 mg, 0.06 mmol) in 1.1 mL THF afforded **38** as only 5% of a mixture of unreacted **24** and other olefinic products in 88% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 90 min, retention times = 57.4 (minor) and 58.7 (major) min.

(*S*,*E*)-6-(But-2-en-2-yl)-2,2,5-trimethyl-3,6-dihydro-2*H*-1,2-oxasiline (39). Following general procedure A, **26** (0.95 g, 4.0 mmol) and **18a** (35 mg, 0.032 mmol) in 72 mL CH_2Cl_2 gave 0.60 g (77% yield) of **39** as a yellow oil (3% EtOAc in hexanes) in 92% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 60 min, retention times = 28.6 (minor) and 29.9 (major) min. $[\alpha]_D^{25}$ = +195.4 ($CHCl_3$, *c* = 0.96). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.69 (dquint, J = 7.7, 1.4 Hz, 1H), 5.49 (q, J = 6.6 Hz, 1H), 4.54 (s, 1H), 1.63 (dd, J = 6.6, 1.1 Hz, 3H), 1.54 (t, J = 1.1 Hz, 3H), 1.51 (s, 3H), 1.29–1.39 (m, 1H), 1.12–1.21 (m, 1H), 0.19 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.9, 136.0, 122.9, 120.4, 83.4, 22.0, 13.5, 12.5, 10.7, 0.3, –0.6. HRMS (EI) *m/z* calc. for $C_{11}H_{20}OSi$: 196.1284, found 196.1281.

(*S*,*Z*)-7-((*E*)-But-2-en-2-yl)-3,3,6-trimethyl-2,3,4,7-tetrahydro-1,3-oxasilepine (40). Following general procedure A, **25** (40 mg, 0.16 mmol) and **18a** (1.7 mg, 0.0016 mmol) in 2.9 mL CH_2Cl_2 gave 21.7 mg (65% yield) of **40** as a yellow oil (2% EtOAc in hexanes)

in 92% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 60 min, retention times = 28.7 (minor) and 29.8 (major) min. $[\alpha]_D^{25}$ = +184.3 ($CHCl_3$, *c* = 0.75). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.66 (t, J = 7.4 Hz, 1H), 5.49 (q, J = 6.9 Hz, 1H), 4.49 (s, 1H), 2.55–2.67 (m, 1H), 2.02–2.12 (m, 1H), 1.68 (t, J = 1.1 Hz, 3H), 1.64 (d, J = 6.9 Hz, 3H), 1.56 (s, 3H), 0.75–0.86 (m, 2H), 0.16 (s, 3H), 0.14 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 137.2, 136.5, 128.8, 121.8, 84.0, 22.6, 21.9, 16.8, 13.5, 11.8, 0.9, –0.3. HRMS (EI) *m/z* calc. for $C_{12}H_{22}OSi$: 210.1440, found 210.1449.

(*S*,*Z*)-2,2,5-Trimethyl-7-((*E*)-2-methylbut-2-enyl)-2,3,6,7-tetrahydro-1,2-oxasilepine (44). Following general procedure B, **35** (40 mg, 0.15 mmol), **8a** (6.0 mg, 0.006 mmol), and NaI (23 mg, 0.15 mmol) in 2.7 mL THF gave 33.1 mg (98% yield) of **44** as a light yellow oil (2% EtOAc in hexanes) in 78% *ee* with <2% of **45** (diagnostic peaks at δ 4.78 (br s, 1H) and 4.72 (br s, 1H) in the ^{1}H NMR spectrum). CP Chirasil-Dex-CB, 1 mL/min, 60 °C for 250 min, retention times = 205.5 (major) and 213.8 (minor) min. $[\alpha]_D^{24}$ = +8.3 ($CHCl_3$, *c* = 0.99). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.53 (t, J = 7.4 Hz, 1H), 5.24 (qq, J = 6.6, 1.1 Hz, 1H), 3.97–4.05 (m, 1H), 2.21–2.36 (m, 2H), 2.01–2.10 (m, 2H), 1.70 (s, 3H), 1.62 (s, 3H), 1.59 (d, J = 6.6 Hz, 3H), 1.54–1.60 (m, 1H), 1.31–1.39 (m, 1H), 0.11 (s, 3H), 0.08 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 134.3, 133.4, 121.3, 121.2, 71.1, 49.2, 41.3, 25.9, 18.0, 16.2, 13.6, 0.4, –1.4. HRMS (EI) *m/z* calc. for $C_{13}H_{24}OSi$: 224.1597, found 224.1598.

(*S*,*E*)-6-(But-2-en-2-yl)-5-methyl-2,2-diphenyl-3,6-dihydro-2*H*-1,2-oxasiline (41). Following general procedure A, **27** (25 mg, 0.069 mmol) and **18a** (1.5 mg, 0.0014 mmol)

in 1.3 mL CH_2Cl_2 gave crude **41** as a pale yellow oil (5% Et_2O in pentane) in 80% *ee*. Chiral SFC (supercritical CO_2 with 5%–50% MeOH ramp over 10 min), ADH, 4 mL/min, 100 bar, 214 nm detector wavelength, retention times = 1.44 (major) and 1.99 (minor) min. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.57–7.64 (m, 4H), 7.32–7.43 (m, 6H), 5.81–5.85 (m, 1H), 5.55 (q, J = 6.6 Hz, 1H), 4.76 (br s, 1H), 1.84 (dq, J = 17.3, 2.8 Hz, 1H), 1.69–1.78 (m, 1H), 1.64 (d, J = 6.6 Hz, 3H), 1.63 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 137.02, 136.62, 136.08, 135.83, 134.73, 134.59, 130.20, 130.07, 128.09, 128.04, 123.32, 120.02, 84.27, 22.20, 13.59, 11.03, 10.50. HRMS (EI) *m/z* calc. for $C_{21}H_{24}OSi$ [M^+] 320.1596, found 320.1597.

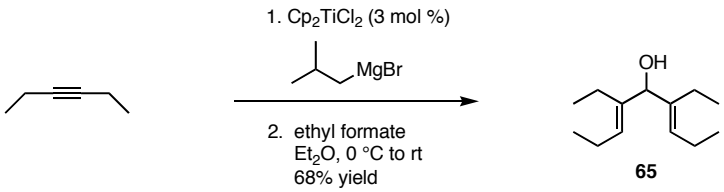
(*E*)-4-Methyl-2-(2-methylbut-2-enyl)-3,6-dihydro-2*H*-pyran (42). Following general procedure B, **34** (23 mg, 0.11 mmol), **8a** (5 mg, 0.005 mmol), and NaI (17 mg, 0.11 mmol) in 2.0 mL THF afforded a crude mixture of **42** (>95%) in 35% *ee* and **43** (<5%) in 38% *ee* (diagnostic peaks at δ 4.78 (br s, 1H) and 4.82 (br s, 1H) in the ^{1}H NMR spectrum). Chiraldex G-TA, 1mL/min, 60 °C for 70 min, retention times = 60.6 (minor) and 62.4 (major) min for **42**, and 25.4 (minor) and 26.2 (major) min for **43**. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) for **42**: δ 5.39 (br s, 1H), 5.26–5.30 (m, 1H), 4.11–4.14 (m, 2H), 3.58–3.67 (m, 1H), 2.32 (dd, J = 13.7, 6.9 Hz, 1H), 2.11 (dd, J = 13.7, 6.3 Hz, 1H), 1.73–1.90 (m, 2H), 1.68 (s, 3H), 1.63 (d, J = 0.8 Hz, 3H), 1.59 (dd, J = 6.9, 0.8 Hz, 3H).

Allyl((2*E*,5*E*)-hepta-2,5-dien-4-yloxy)dimethylsilane (48). To a solution of imidazole (486 mg, 7.1 mmol) in DMF (5 mL) was added the known alcohol (2*E*,5*E*)-hepta-2,5-dien-4-ol[27] (200 mg, 1.8 mmol) and allylchlorodimethylsilane (0.40 mL, 2.7 mmol).

After 16 h at rt, the reaction mixture was diluted with 10 mL of water and extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with aqueous 1 M $CuSO_4$, water, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (2% ethyl acetate in hexanes) afforded 253 mg (67% yield) of **48** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.72–5.86 (m, 1H), 5.54–5.65 (m, 2H), 5.42–5.50 (m, 2H), 4.83–4.92 (m, 2H), 4.52 (tquint, J = 6.0, 0.8 Hz, 1H), 1.68 (dt, J = 6.0, 0.8 Hz, 6H), 1.62 (dt, J = 8.0, 1.1 Hz, 2H), 0.11 (s, 6H). Upon exposure to olefin metathesis catalyst **50**, it was completely converted into a complex mixture of volatile products.

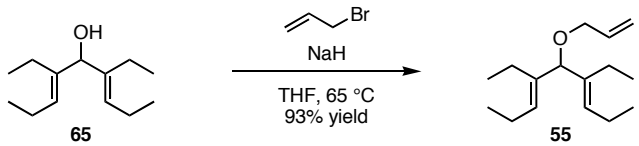
((2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-yloxy)dimethyl(vinyl)silane (51). To a solution of **21** (0.50 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (1.5 mL, 11 mmol) and chlorodimethylvinylsilane (0.98 mL, 7.1 mmol). After 12 h at rt, the light brown reaction mixture was poured into 20 mL of water and was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with water, brine, dried over Na_2SO_4, and concentrated. Purification by flash chromatography (100% hexanes) afforded 0.70 g (88% yield) of **51** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.11 (dd, J = 20.1, 14.8 Hz, 1H), 5.95 (dd, J = 14.8, 4.4 Hz, 1H), 5.73 (dd, J = 20.1, 4.4 Hz, 1H), 5.52 (qquint, J = 6.6, 1.4 Hz, 2H), 4.30 (br s, 1H), 1.61 (dt, J = 6.6, 1.1 Hz, 6H), 1.42 (t, J = 1.1 Hz, 6H), 0.14 (s, 6H). Upon exposure to olefin metathesis catalyst **50**, only a small amount was converted into the desired product **52**; most of the **51** did not react.

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-yl acrylate (53). To a solution of *N*,*N*-dimethylaminopyridine (87 mg, 0.71 mmol), **21** (200 mg, 1.4 mmoml), and acrylic acid (0.29 mL, 4.3 mmol) in CH_2Cl_2 at 0 °C was added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDC) (820 mg, 4.3 mmol) and triethylamine (0.60 mL, 4.3 mmol). After 15 min at 0 °C, the orange mixture was allowed to warm to rt, where it stirred for 3 days. It was diluted with 25 mL diethyl ether and 25 mL water, and was extracted with ether (3 × 30 mL). The combined organic layers were washed with aqueous 1 N HCl, water, brine, dried over $MgSO_4$, and concentrated. Purification by flash chromatography (4% ethyl acetate in hexanes) afforded 152 mg (55% yield) of **53** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.42 (dd, J = 17.3, 1.6 Hz, 1H), 6.15 (dd, J = 17.3, 10.4 Hz, 1H), 5.82 (dd, J = 10.2, 1.6 Hz, 1H), 5.55 (tq, J = 6.6, 1.4 Hz, 2H), 5.51 (br s, 1H), 1.64 (dt, J = 6.6, 1.1 Hz, 6H), 1.54 (t, J = 1.1 Hz, 6H). Upon exposure to olefin metathesis catalyst **50**, it was completely converted to a complex mixture of unseparated products that had many vinylic hydrogen atoms.



(3*E*,6*E*)-4,6-Diethylnona-3,6-dien-5-ol (65). To a solution of 3-hexyne (1.4 mL, 1.0 g, 12.2 mmol) and isobutylmagnesium bromide (2.0 M in Et_2O, 6.1 mL, 12.2 mmol) in 12 mL of Et_2O was added titanocene dichloride (85 mg, 0.34 mmol). After 1 h at rt, the solution was cooled to 0 °C and ethyl formate (0.44 mL, 0.40 g, 5.5 mmol), in 0.5 mL Et_2O, was added dropwise. After 5 min at 0 °C, the solution was allowed to warm to rt.

After 1 h at rt, the reaction was quenched with saturated aqueous ammonium chloride (carefully; bubbling occurred), and it was filtered through a pad of celite, which was washed with water and diethyl ether. The organic layer was removed from the filtrate, and the remaining aqueous layer was extracted with 2 × Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated. Purification by flash chromatography (10% ethyl acetate in hexanes) afforded 0.73 g (68% yield) of **65** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.47 (t, J = 7.2 Hz, 2H), 4.45 (br s, 1H), 1.98–2.13 (m, 6H), 1.81–1.93 (m, 2H), 1.44 (br s, 1H), 1.00 (t, J = 7.4 Hz, 6H), 0.94 (t, J = 7.4 Hz, 6H).



65 55

(3*E*,6*E*)-5-(Allyloxy)-4,6-diethylnona-3,6-diene (55). To a suspension of 95% NaH (24 mg, 1.0 mmol) in 1.5 mL of THF was added **65** (100 mg, 0.51 mmol). After 10 min at rt, allyl bromide (filtered through neutral alumina, 66 μL, 0.76 mmol) was added. After 16 h at 65 °C, the reaction mixture was diluted with 10 mL Et_2O, carefully quenched with 10 mL of water, and extracted with 3 × 20 mL of Et_2O. The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. Purification by flash chromatography (1% ethyl acetate in hexanes) afforded 112 mg (93% yield) of **55** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.86–5.99 (m, 1H), 5.45 (t, J = 7.2 Hz, 2H), 5.26 (dq, J = 17.3, 1.9 Hz, 1H), 5.10–5.16 (m, 1H), 4.00 (br s, 1H), 3.89 (dt, J = 5.5, 1.4 Hz, 2H), 1.96–2.14 (m, 6H), 1.78–1.90 (m, 2H), 0.99 (t, J = 7.4 Hz, 6H), 0.92 (t, J = 7.4 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.45, 135.67, 129.25, 116.20, 86.02,

68.92, 21.10, 20.61, 14.66, 14.20. HRMS (EI) *m/z* calc. for $C_{16}H_{28}O$ [M^+] 236.2140, found 236.2140.

(*E*)-3-Ethyl-2-(hex-3-en-3-yl)-2,5-dihydrofuran (56). Following general procedure B, **55** (12 mg, 0.050 mmol), **8a** (2 mg, 0.0020 mmol), and NaI (7.5 mg, 0.050 mmol) in 0.9 mL THF gave a crude residue that was passed down a pipet column (5% ethyl acetate in hexanes) to afford **56** (>95% conv.) in 29% *ee*. Chiraldex G-TA, 1mL/min, 50 °C for 15 min, retention times = 2.7 (major) and 3.1 (minor) min. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.55–5.57 (m, 1H), 5.36 (t, J = 14.6 Hz, 1H), 4.95 (br s, 1H), 4.65–4.72 (m, 1H), 4.56–4.62 (m, 1H), 1.80–2.13 (m, 6H), 1.07 (t, J = 7.4 Hz, 3H), 0.99 (t, J = 7.4 Hz, 3H), 0.97 (t, J = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 144.12, 140.19, 131.73, 119.40, 94.54, 75.51, 21.13, 20.36, 19.40, 15.01, 14.55, 12.03. HRMS (EI) *m/z* calc. for $C_{12}H_{20}O$ [M^+] 180.1514, found 180.1510.

References

[1] For recent reviews on asymmetric olefin metathesis, see (a) Hoveyda, A. H. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 2.3. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633. (c) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945–950.

[2] La, D. S.; Alexander, J. B.; Cefalo, D. R.; Graf, D. D.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1998**, *120*, 9720–9721.

[3] Zhu, S. S.; Cefalo, D. R.; La, D. S.; Jamieson, J. Y.; Davis, W. M.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc.* **1999**, *121*, 8251–8259.

[4] Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225–3228.

[5] (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502–12508. (b) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955. (c) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2005**, *127*, 6877–6882.

[6] (a) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2004**, *126*, 12288–12290. (b) ref. 5.

[7] The best result for ARCM with catalysts **9** and **10** is a 77% *ee*, and in many cases 10 mol % of the catalyst is needed.

[8] Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. *Submitted*, **2006**.

[9] A portion of this work is published: Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840–1846.

[10] Wolfe, J. P.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1144–1157.

[11] (a) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85–88. (b) Garner, C. M.; Prince, M. E. *Tetrahedron Lett.* **1994**, *35*, 2463–2464.

[12] Han, S.-Y. and Chang, S. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 2.2.

[13] (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

[14] One mol % of **18a** is added at the beginning of the reaction, and another 1 mol % is added after 2 h. When 2 mol % of **18a** is added at the start with no subsequent additions, the yield was only 74%. For more information, see ref. 9.

[15] See appendix 1 for an interesting side product formed during ARCM of **47**.

[16] (a) Hong, S. H.; Day, M. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2004**, *126*, 7414–7415. (b) Ulman, M.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 7202–7207.

[17] (a) Pietraszuk, C.; Marciniec, B.; Fischer, H. *Organometallics* **2000**, *19*, 913–917. (b) Pietraszuk, C.; Fischer, H. *Chem. Commun.* **2000**, 2463–2464. (c) Pietraszuk, C; Fischer, H. *Organometallics* **2001**, *20*, 4641–4646.

[18] Teng, X.; Cefalo, D. R.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 10779–10784.

[19] Morgan, J. P. Ph.D. Thesis, California Institute of Technology, 2002.

[20] Evidence for cis coordination: (a) Trnka, T. M.; Day, M. W.; Grubbs, R. H. *Organometallics* **2001**, *20*, 3845–3847. Evidence for trans coordination: (b) Tallarico, J. A.; Bonitatebus, Jr., P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157–7158. (c) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032-5033.

[21] (a) Costabile, C.; Cavallo, L. *J. Am. Chem. Soc.* **2004**, *126*, 9592–9600. (b) Adlhart, C.; Chen, P. *J. Am. Chem. Soc.* **2004**, *126*, 3496–3510. (c) Fomine, S.; Vargas, S. M.; Tlenkopatchev, M. A. *Organometallics* **2003**, *22*, 93–99. (d) Cavallo, L. *J. Am. Chem. Soc.* **2002**, *124*, 8965–8973. (e) Vyboishchikov, S. F.; Bühl, M.; Thiel, W. *Chem. Eur. J.* **2002**, *8*, 3962–3975.

[22] This explanation is directly related to the Curtin-Hammett principle. For more information, see Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

[23] Another explanation is that the reaction proceeds through a late, product-like transition state when the less active diiodide catalysts are used. A higher degree of stereochemical communication would be expected for a late transition state. For evidence of this affect

derived from electronic changes to a catalyst, see Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc*. **1998**, *120*, 948–954.

[24] Kiely, A. F.; Jernelius, J. A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 2868–2869.

[25] Robertson, J.; Hall, M. J.; Stafford, P. M.; Green, S. P. *Org. Biomol. Chem*. **2003**, *1*, 3758–3767.

[26] Kunai, A.; Kawakami, T.; Toyoda, E.; Ishikawa, M. *Organometallics* **1992**, *11*, 2708-2711.

[27] Underiner, T. L.; Goering, H. L. *J. Org. Chem*. **1990**, *55*, 2757–2761.

Chapter 5
Total Synthesis of (+)-5-*Epi*-Citreoviral Using Ruthenium-Catalyzed Asymmetric Ring-Closing Metathesis

If carbonyl compounds have been said to be 'virtually the backbone of organic synthesis,' the epoxides correspond to at least 'one of the main muscles.'[1]

Introduction

(+)-Citreoviral (**1**) was first isolated from *Penicillium citreoviride* in 1984,[2] and a year later its absolute configuration was determined (Figure 5.1).[3] Other structurally similar metabolites have been isolated from the same fungus (**3** and **4**),[4] and most have been found to be potent inhibitors of mitochondrial ATPase and oxidative phosphorylation.[5] The 2,6-dioxabicyclo[3.2.1]octane core of citreoviridinol (**4**) is also found in the aurovertin family of compounds, which exhibit a similar biological profile to the *P. citreoviride* metabolites.[6]

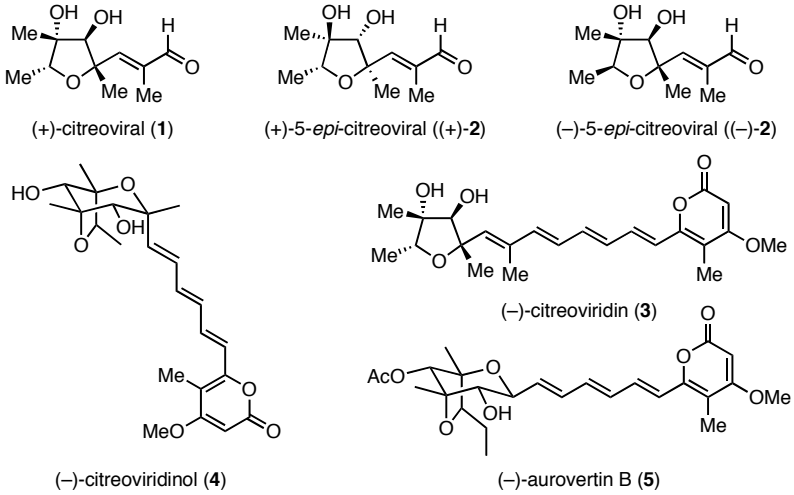
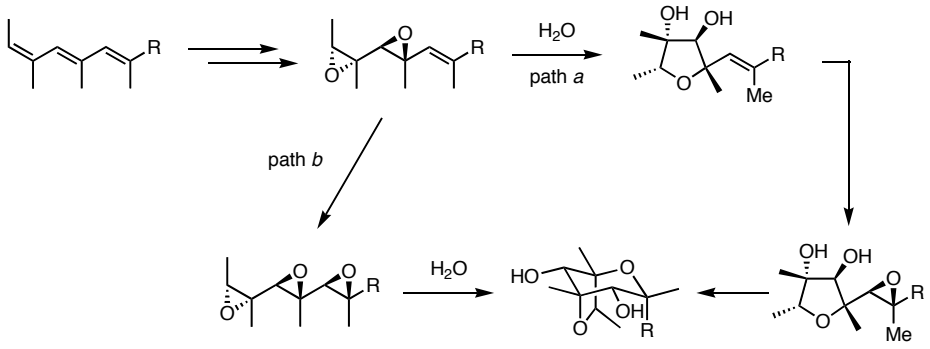


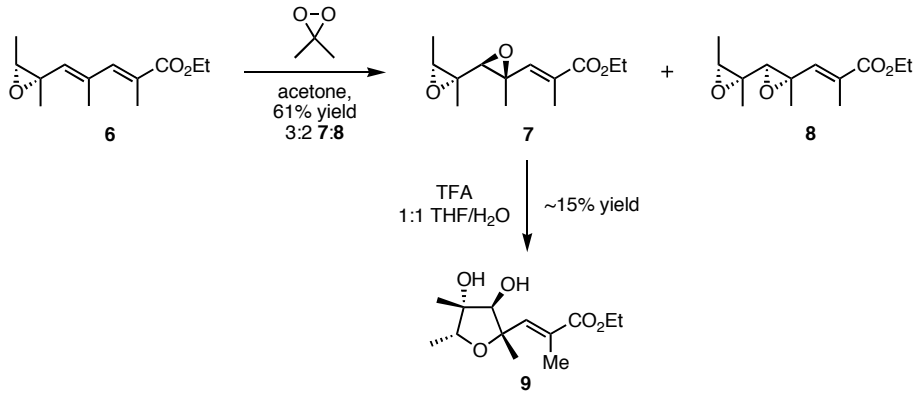
Figure 5.1. Members of a family of structurally related compounds.

The biosynthesis of **1** and **3** has been postulated to occur through a bis-epoxide that is attacked by water to yield the substituted tetrahydrofuran found in the natural product (Scheme 5.1, path *a*).[7,8] Epoxidation of the vinyl-substituted product followed by an intramolecular epoxide opening would lead to the 2,6-dioxabicyclo[3.2.1]octane core found in citreoviridinol and the aurovertins.[9] Alternatively, a tris-epoxide could be opened under aqueous conditions to yield the 2,6-dioxabicyclo[3.2.1]octane core in one biosynthetic operation (path *b*).[10]



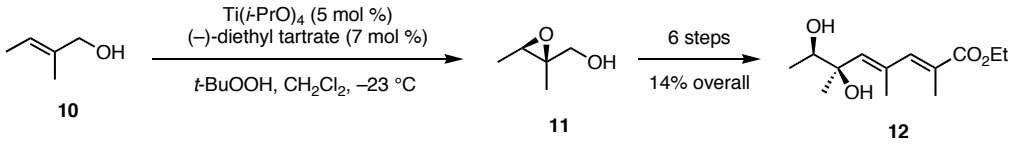
Scheme 5.1. Proposed biosynthesis of citreoviral, citreoviridin, and related structures.

Support for the proposed biosyntheses of these molecules has been provided through various syntheses of citreoviral, citreoviridin, and citreoviridinol.[11] In these cases, bis-epoxides or 1,2-diols with adjacent epoxides have reacted under acidic conditions to yield substituted tetrahydrofurans (Scheme 5.2). Further manipulation of the product by epoxidation and intramolecular ring opening (as illustrated in Scheme 5.1, path *a*) formed the desired 2,6-dioxabicyclo[3.2.1]octane core. These syntheses support the stepwise formation of citreoviridinol from citreoviral or citreoviridin. There have been no examples where a linear bis- or tris-epoxide has led to the 2,6-dioxabicyclo[3.2.1]octane core in one step.



Scheme 5.2. An example of a biomimetic synthesis of the tetrahydrofuran core (ref 10).

In addition to the biomimetic syntheses mentioned above, racemic and enantioenriched citreoviral has been made a number of other ways as well.[12] Of the asymmetric syntheses, all but one method use either a chiral auxiliary,[13] chiral reagents,[14] or a chiral, non-racemic starting material.[15] The only catalytic asymmetric report was a formal total synthesis, where a Sharpless asymmetric epoxidation was used to ultimately yield **12**, which is a known intermediate en route to citreoviral (Scheme 5.3).[16] Racemic forms of unnatural 3-*epi*-citreoviral[17] and 5-*epi*-citreoviral[18] have also been synthesized.

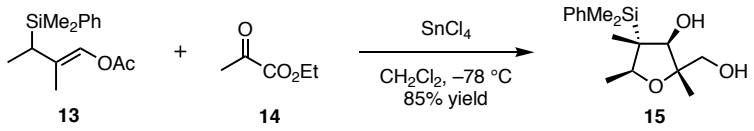


Scheme 5.3. Formal synthesis of (+)-citreoviral using asymmetric catalysis.

The interest in the synthesis of this class of compounds is due to their biological activity and the complexity of the tetrahydrofuran and 2,6-dioxabicyclo[3.2.1]octane cores. The formation of the desired cyclic structures with complete control over the stereochemistry is challenging, and the key step in many of the known syntheses is the generation of the ring system. Achieving not only diastereocontrol but also control of the

absolute stereochemistry is more challenging still, and it has been accomplished using asymmetric catalysis only once.

The previous chapter contains a study on ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM), and the present chapter illustrates how ARCM was used to complete the first asymmetric total synthesis of (+)-5-*epi*-citreoviral ((+)-**2**). 5-*Epi*-citreoviral has only been synthesized once previously as a racemate, and the approach that was used to generate the tetrahydrofuran ring was a [3 + 2] annulation reaction between an allyl silane and a ketone (Scheme 5.4).[18] The synthesis described in the current chapter utilizes ARCM and an acid-catalyzed cascade epoxide opening as key steps. Additionally, the high-yield, single-step preparation of a diastereomer of the 2,6-dioxabicyclo[3.2.1]octane core found in citreoviridinol (**4**) from an intramolecular cascade epoxide-opening reaction will be discussed.

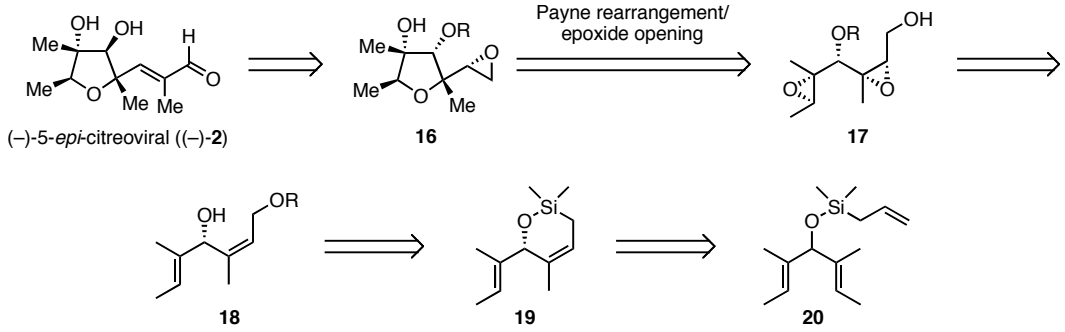


Scheme 5.4. [3 + 2] Annulation reaction to form an intermediate in the synthesis of (±)-5-*epi*-citreoviral.

Retrosynthetic Analysis

One of the most successful ARCM substrates used in the chiral, Ru-catalyzed reaction is **20**. Low catalyst loadings (≤1 mol %) can be used to obtain **19** in 92% *ee*, which makes **20** a practical starting material in the synthesis of 5-*epi*-citreoviral. It was envisioned that (–)-5-*epi*-citreoviral ((–)-**2**) could be made from tetrahydrofuran **16**, which could ultimately originate from **20** as illustrated in Scheme 5.5. The key steps in

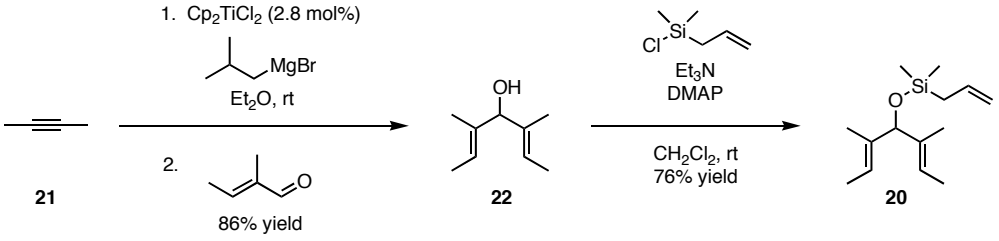
the proposed synthesis are the substrate-directed bis-epoxidation (**18** to **17**) and the Payne rearrangement/epoxide opening reaction (**17** to **16**).



Scheme 5.5. Retrosynthesis of (–)-5-*epi*-citreoviral to ARCM substrate **20**.

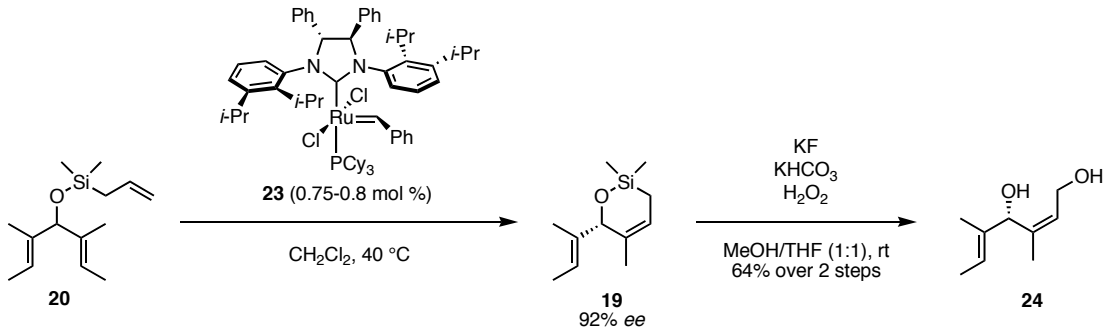
Results and Discussion

The ARCM substrate **20** was synthesized as described in the previous chapter (Scheme 5.6). The alcohol precursor **22** is available in multigram quantities in one step from 2-butyne (**21**) and tiglic aldehyde,[19] and the silyl ether **20** can be formed using standard conditions. Compound **20** is unstable to silica gel chromatography; within a minute of being applied to a silica gel column, the pale yellow oil becomes purple and an exothermic decomposition occurs. Attempts to distill the product gave impure material that would not undergo ARCM. Fortunately, the product is relatively stable to filtration through neutral alumina, and could be isolated in high purity in 76% yield.



Scheme 5.6. Synthesis of ARCM substrate **20**.

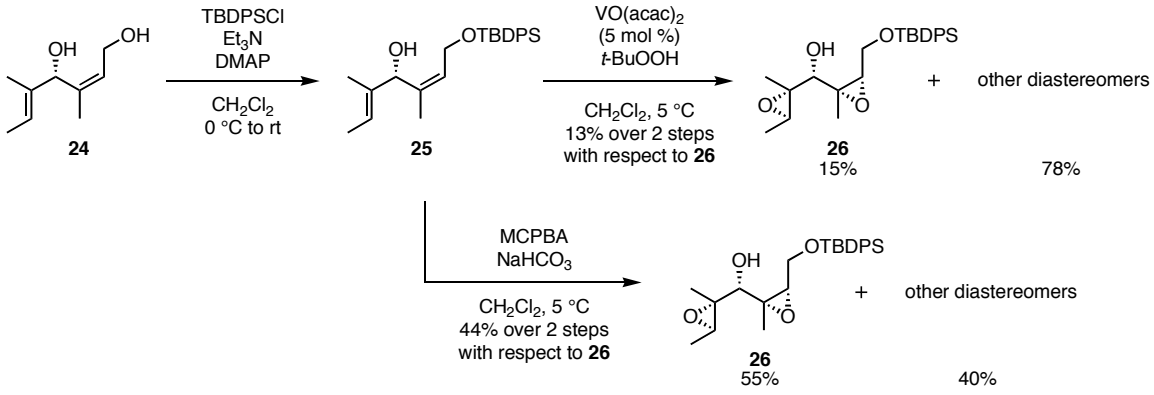
ARCM was preformed multiple times on approximately 1g of **20** using 0.75–0.8 mol % of catalyst **23**. None of the starting material was detected by TLC after 2 h (Scheme 5.7). The cyclic product **19** had an enantiomeric excess of 92%, and the absolute stereochemistry was determined as discussed in chapter 4 of this dissertation. After removal of the ruthenium-containing by-products via silica gel chromatography, **19** was subjected to a Tamao-Fleming oxidation to form diol **24** in 64% yield over two steps.[20] It has been reported that a sequential olefin metathesis/Tamao-Fleming oxidation process is possible without the need for purification,[21] but attempts to oxidize **19** to **24** without removing the ruthenium by-products resulted in an exothermic decomposition of hydrogen peroxide and no oxidation of **19**.



Scheme 5.7. Synthesis of enantioenriched diol **24** by ARCM.

Due to the different steric environments of the two hydroxyl groups in **24**, selective protection of the primary alcohol in the presence of a secondary alcohol was readily achieved. As illustrated in Scheme 5.8, installation of a *t*-butyldiphenylsilyl group occurred in high yield to afford compound **25**, which was isolated with a silicon-containing compound (most likely *t*-butyldiphenylsilanol) as a minor impurity (~7:1) that could not be removed by flash chromatography. At this point in the synthesis, only a single chiral center was present in the molecule, and its absolute stereochemistry was set

using ARCM. It was envisioned that all of the remaining chiral centers could be installed in a single, substrate-directed bis-epoxidation reaction.



Scheme 5.8. Acyclic substrate-directed epoxidation of secondary alcohol **25**.

Treatment of allyl alcohol **25** with catalytic $VO(acac)_2$ and *t*-butyl hydroperoxide as the stoichiometric oxidant resulted in a mixture of diastereomers, including the desired product **26** (Scheme 5.8, upper pathway). No starting material was present after 12 hours, and three products were isolated (separated by column chromatography) from the reaction mixture in an overall yield of approximately 93%. Due to the small amount of an impurity in alcohol **25**, the exact yield for the epoxidation reaction was not available. The ^{1}H NMR spectra of all three of the isolated products were consistent with epoxidation of both alkenes. Fortunately, the racemate of one of the diastereomers was a crystalline solid, and X-ray crystallography showed that it was the desired bis-epoxide **26** (Figure 5.2). Unfortunately, it was one of the minor products (15% of the recovered mass). The two other diastereomers were isolated in 74% and 4% yields, and the relative stereochemistry of the two products was not determined.

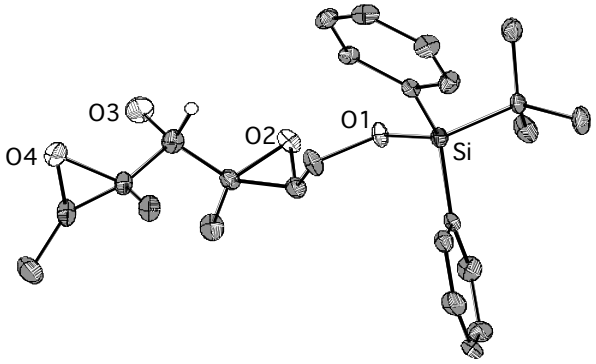


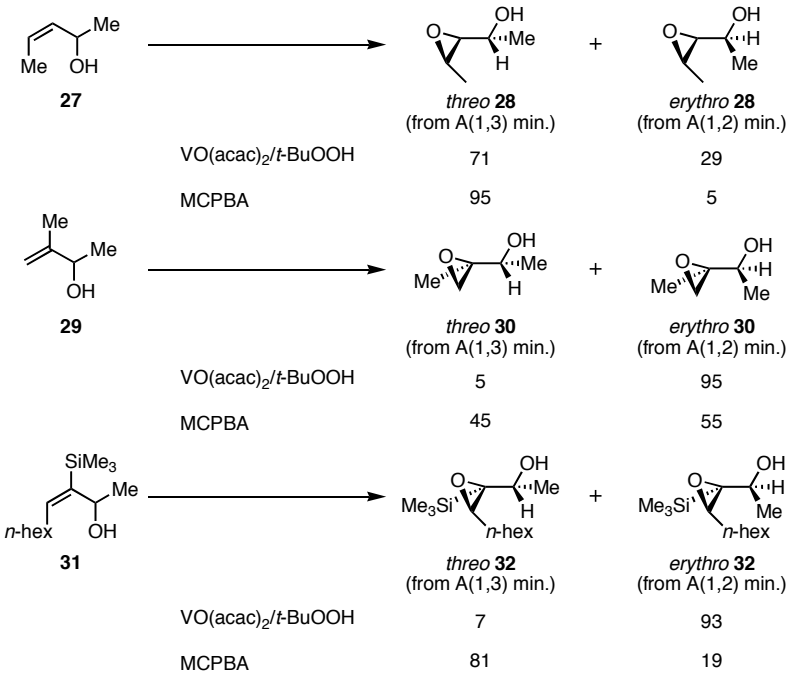
Figure 5.2. Structure of **26** with displacement ellipsoids drawn at 50% probability.

The overall yield for the formation of **26** from **24** using $VO(acac)_2$ and *t*-BuOOH was only 13%, so an alternative epoxidation procedure was examined. Treatment of **25** with buffered MCPBA at 5 °C generated all four of the possible bis-epoxide diastereomers in a different ratio than was obtained above (Scheme 5.8, lower pathway). In this case, the major product (55% of the recovered mass) was the desired compound **26**, resulting in a 44% yield over 2 steps. As with the metal-catalyzed epoxidation, no starting material was present after 12 hours, and only bis-epoxide products were isolated. Synthetically useful amounts of **26** could be produced using this procedure, with the stereochemistry at four chiral centers (three of which are present in the final product) being set in a single reaction.

A stereochemical rationale was sought in order to understand why the two epoxidation procedures led to different product distributions. In general, when there is a cis allylic olefin (**27**), MCPBA favors the product derived from A(1,3) strain minimization (*threo* **28**) to a greater extent than the vanadium conditions (Scheme 5.9).[22] On the other hand, $VO(acac)_2$/*t*-BuOOH favors the product derived from A(1,2) strain minimization more than MCPBA when the allylic alcohol has substitution at the internal position of the alkene (**29**). When there is substitution in both positions (**31**), the

vanadium-catalyzed reaction favors the product derived from A(1,2) strain minimization (*erythro* **32**), and MCPBA favors the product derived from A(1,3) strain minimization (*threo* **32**).

Sharpless proposed O=C–C=C dihedral angles for both the vanadium-catalyzed and MCPBA reactions based on the data shown in Scheme 5.9, and the preferred conformations are shown in Figure 5.3.[22b] The $VO(acac)_2$/*t*-BuOOH procedure has a favored dihedral angle of ~50 °; therefore if R_1 and R_2 are large groups, conformation **33** will higher in energy than **34**, and the *erythro* product will be preferred regardless of R_3. Due to the larger dihedral angle in the MCPBA reaction, R_1 interacts more with R_3 than R_2. Therefore, when R_1 and R_3 are large, conformation **35** (*threo* product) will be favored. These models are consistent with the products observed in the epoxidation of **31** shown in Scheme 5.9.



Scheme 5.9. Comparison of stereoselective epoxidation methods using substituted allylic alcohols (ref 22).

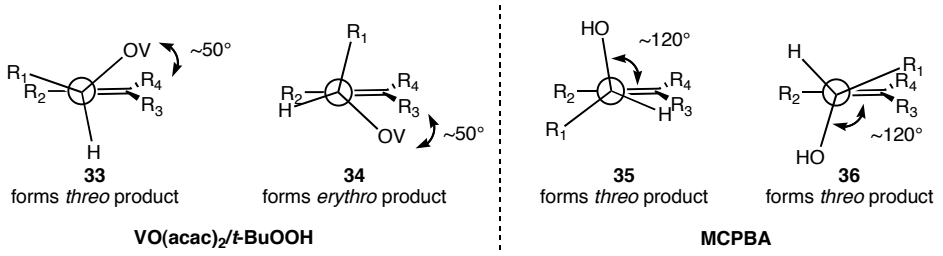
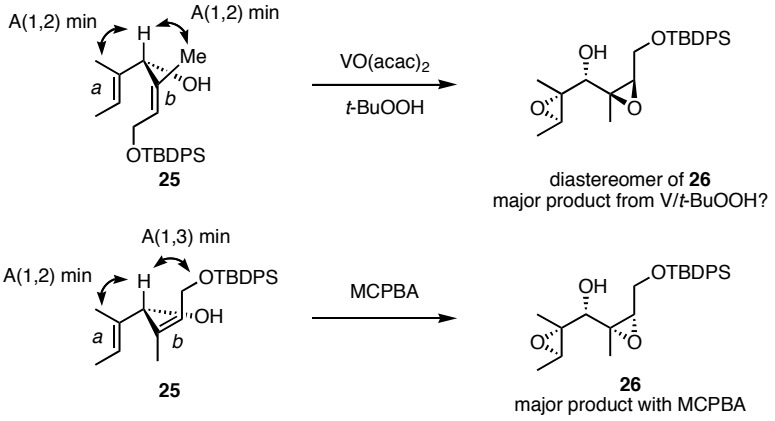


Figure 5.3. Proposed O=C–C=C dihedral angles for vanadium-catalyzed and MCPBA epoxidations.

It is possible to rationalize the difference in diastereoselectivity between the two epoxidations shown in Scheme 5.8 by looking at each olefin in 25 individually and comparing them to the model systems described above. In the desired product **26**, one epoxide needs to come from an A(1,2) strain-minimized configuration and one from an A(1,3) strain-minimized configuration (Scheme 5.10). Olefin *a* in substrate **25** does not have a cis methyl group, and therefore the A(1,2) interaction should minimized. Olefin *b* has substituents in the cis position and on the carbon adjacent to the alcohol, so both A(1,2) and A(1,3) strain is present.

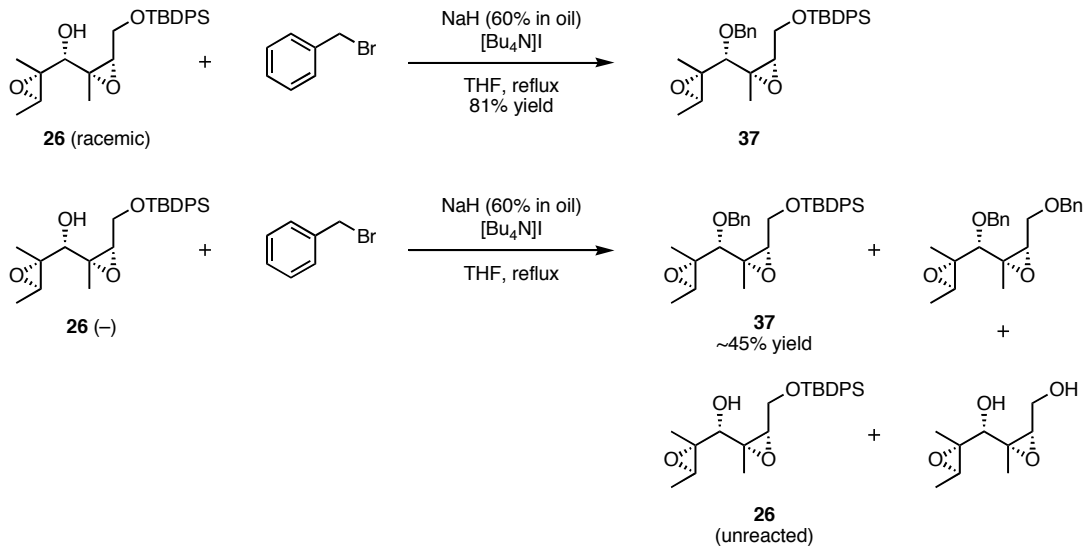


Scheme 5.10. Proposed configurations leading to bis-epoxides.

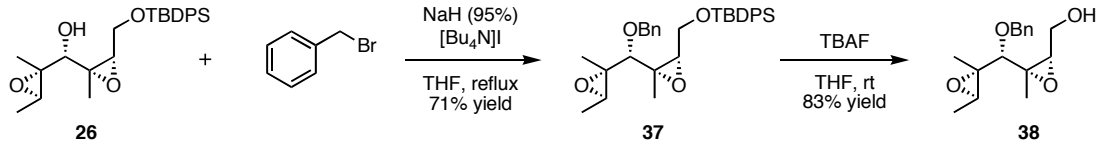
When $VO(acac)_2$/*t*-BuOOH is used as the oxidant, olefin *a* resembles model substrate **29**, and the desired epoxide (from A(1,2) minimization) should be strongly preferred. Compound **31** is most like olefin *b*, and the vanadium conditions are expected

to favor minimization of the A(1,2) strain to yield the diastereomer of **26** shown in Scheme 5.10. The MCPBA epoxidations would be expected to proceed with different levels of selectivity for each olefin oxidation relative to the vanadium reaction. The major oxirane from the epoxidation of olefin *a* should be the same as in the $VO(acac)_2$/*t*-BuOOH reaction, but the selectivity is expected to be lower based on the oxidation of model compound **29**. When olefin *b*, which resembles **31**, is treated with MCPBA, the opposite face of the alkene is expected to be epoxidized, because A(1,3) strain is preferentially minimized. Overall, the presence of **26** as the major product with MCPBA can be rationalized by treating each alkene as a separate allylic alcohol and predicting the relative stereochemistry using the proposed configurations discussed above.

With compound **26** in hand, the Payne rearrangement/epoxide-opening substrate **17** was the targeted intermediate. Attempts to protect the secondary alcohol as a *p*-methoxybenzyl (PMB) ether using a variety of conditions resulted in either no reaction or substrate decomposition. Alternatively, protection with benzyl bromide using NaH (60% in oil) as a base led to benzyl ether **37** (Scheme 5.11). These conditions were initially developed using racemic **26**; when the same conditions were used a few months later with enantioenriched **26**, a mixture of products was isolated. The ^{1}H NMR spectrum of enantioenriched **26** looked identical to that of the racemate, so it was expected that water or NaOH from the 60% NaH in oil may be contaminating the reaction and causing a hydroxide-mediated deprotection of the silyl ether. By using dry NaH in place of 60% NaH in oil, **37** was isolated in 71% yield (Scheme 5.12). Deprotection of the primary alcohol using tetrabutylammonium fluoride proceeded uneventfully to yield the Payne rearrangement/epoxide-opening substrate **38**.



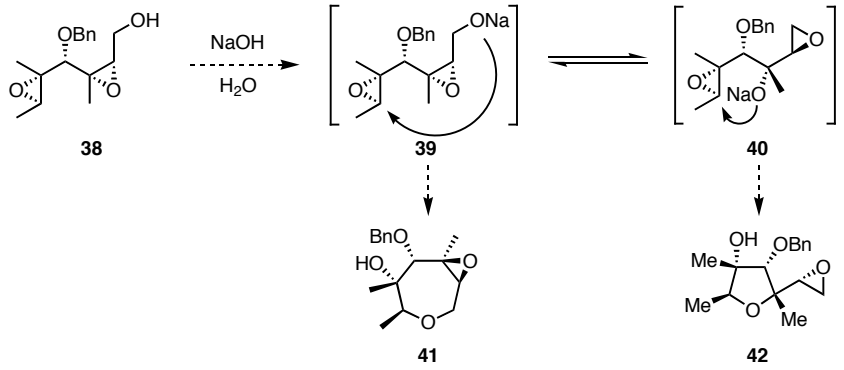
Scheme 5.11. Benzyl ether formation using fresh (upper) and aged (lower) NaH (60% in oil).



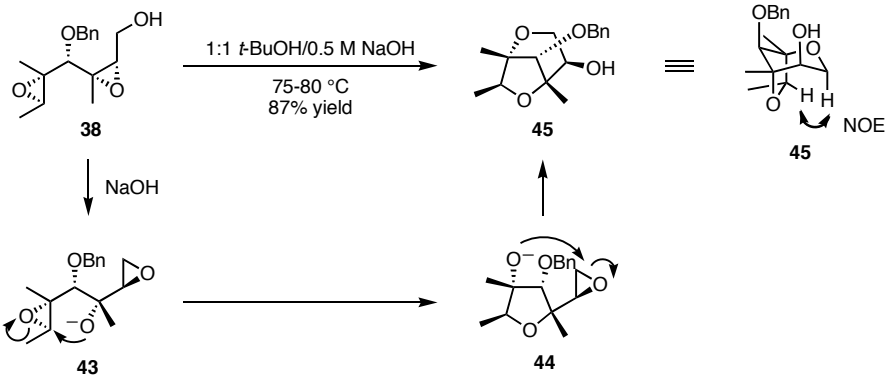
Scheme 5.12. Synthesis of bis-epoxide intermediate **38**.

It was envisioned that, upon exposure to aqueous base, compound **38** would undergo a Payne rearrangement.[23] An equilibrium of epoxy alcohols is typically formed, but internal trapping of alkoxide **40** could occur to form 5-membered ring **42** (5-endo-tet) that should be favored over a seven-membered ring derived from **39** (Scheme 5.13). When **38** was treated with aqueous NaOH at 80 °C, a single compound was isolated in 87% yield. The ^{1}H NMR spectrum contained no oxirane methylene hydrogens, and a secondary alcohol was present (based on the coupling of hydroxyl hydrogens in DMSO-d_6), indicating the desired product was not formed. Instead of **42**, the isolated product was **45**, and NOE experiments supported this structure. A proposed mechanism for the formation of **45** is shown in Scheme 5.14. The first two steps are consistent with the

mechanism in Scheme 5.13, but a second intramolecular epoxide-opening reaction occurs to give the bicyclic product.



Scheme 5.13. Proposed synthesis of **42** using a Payne-rearrangement/epoxide opening process.

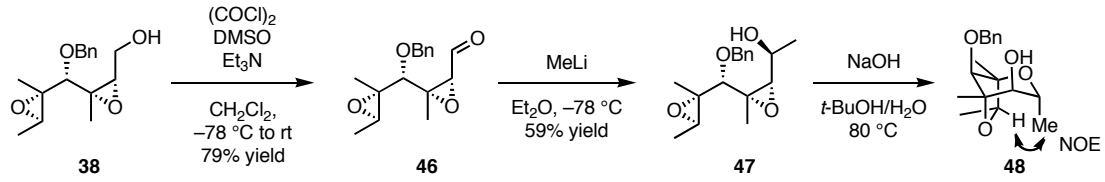


Scheme 5.14. Payne rearrangement/cascade epoxide opening sequence to form **45**.

Although compound **45** was not the desired product, it is a 2,6-dioxabicyclo[3.2.1]octane ring system and is a diastereomer of the core found in citreoviridinol and the aurovertins. Its formation here may provide insight into the biosynthesis of these families of natural products. Scheme 5.2 illustrates an epoxide opening sequence that is thought to mimic the biosynthesis of the substituted tetrahydrofuran found in citreoviral and citreoviridin. The same approach with a tris-epoxide has not been shown,[10,24] and all biomimetic synthetic approaches to compounds containing a 2,6-dioxabicyclo[3.2.1]octane core have gone through an isolated,

substituted tetrahydrofuran intermediate.[25] The high yield and stereospecificity (only one stereoisomer was observed) of the reaction in Scheme 5.14 suggest that the natural products with 2,6-dioxabicyclo[3.2.1]octane cores maybe be formed in a single step from a tris-epoxide (Scheme 5.1, path *b*).

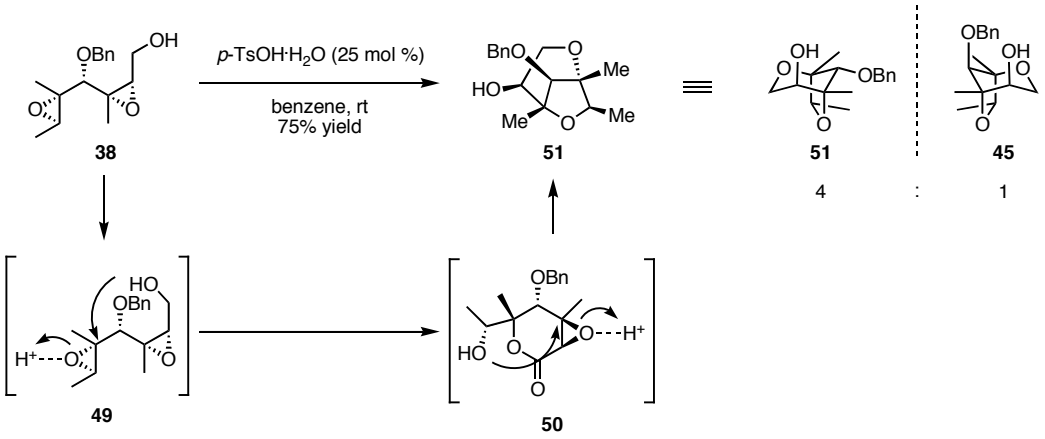
In an attempt to explore if the above route could be used to synthesize citreoviridinol, the aurovertins, or diastereomers of these natural products, substitution was introduced to **45** in the appropriate position. Primary alcohol **38** was transformed into an aldehyde with a Swern oxidation, and methyllithium was added to yield secondary alcohol **47** (Scheme 5.15). This reaction was done on 7.5 mg, and only one diastereomer was isolated. Compound **47** was treated under the same conditions as the formation of **45**, and a single product (**48**) was observed. This result illustrates that the Payne rearrangement/cascade epoxide opening sequence could be used to make citreoviral, the aurovertins, or stereoisomers of these biologically active natural products.



Scheme 5.15. Formation of a substituted 2,6-dioxabicyclo[3.2.1]octane ring system.

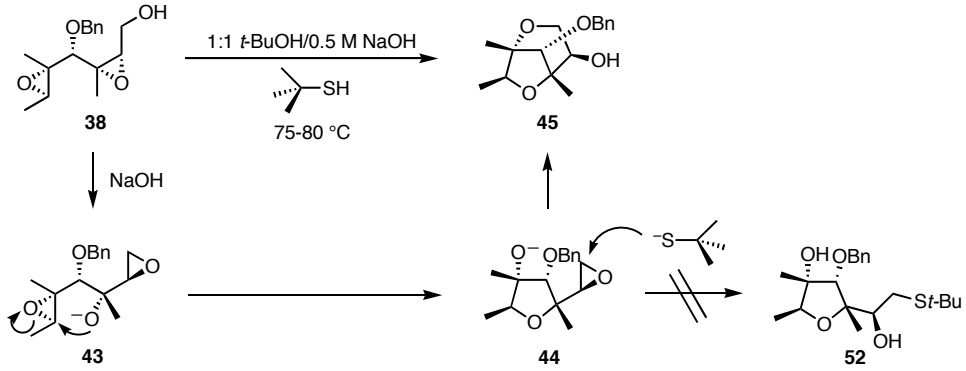
It was thought that if the formation of **45** occurred as illustrated in Scheme 5.14, treatment of **38** with acid could result in a reaction where the epoxides are opened at the more sterically hindered positions. Gratifyingly, a catalytic amount of *p*-toluenesulfonic acid caused **38** to undergo an intramolecular reaction to yield a mixture of **51** and **45** (Scheme 5.16). Compound **51** is derived from the expected epoxide opening at the more hindered position and is a pseudoenantiomer of **45**. This result suggests that both

enantiomers of compounds containing 2,6-dioxabicyclo[3.2.1]octane cores could be made from a single enantiomer.



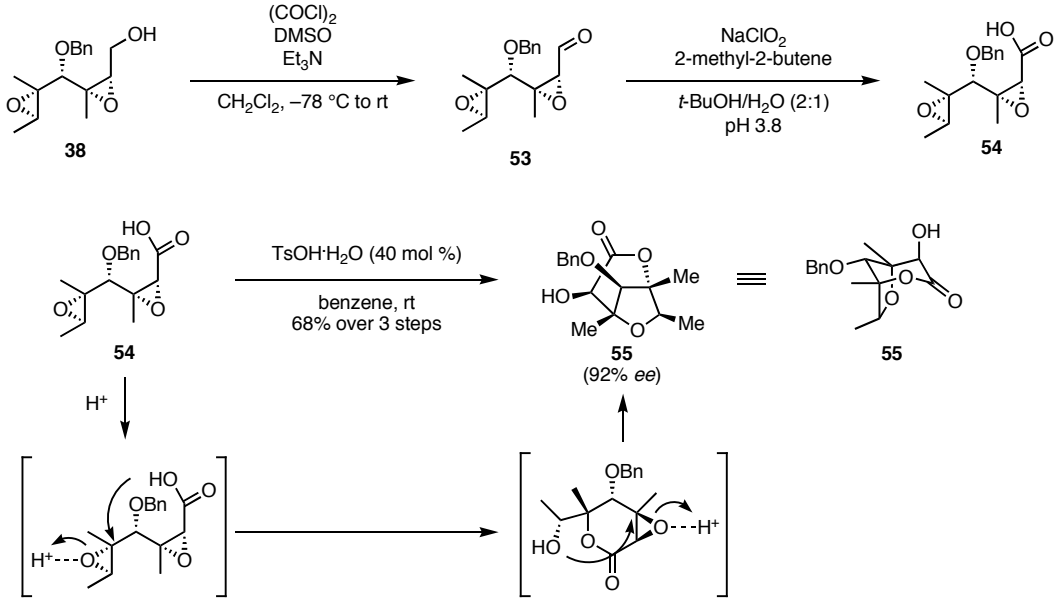
Scheme 5.16. Acid-catalyzed formation of 2,6-dioxabicyclo[3.2.1]octane ring system.

Although the formation of 2,6-dioxabicyclo[3.2.1]octane cores was exciting, it was not obvious how to synthetically transform **45** or **51** into (–)-5-*epi*-citreoviral. The six-membered ring ether needed to be opened to access a substituted tetrahydrofuran that was not part of a bicyclic system. Unfortunately, ethers are typically synthetically inert under all but extreme conditions. Attempts to intercept intermediate **44** with *t*-butyl thiolate so the six-membered ring could not form were unsuccessful (Scheme 5.17);[26] the cascade epoxide-opening reaction was too efficient.



Scheme 5.17. Failed attempt to intercept intermediate **44**.

It was finally decided that, because the cascade epoxide-opening reaction under both basic and acidic conditions was efficient and high yielding, the use of an alternative substrate could allow for further functionalization. The pyranyl rings in **45** and **51** would not be easily cleaved, but a lactone can be readily opened. Therefore, carboxylic acid **54** was made by a two-stage oxidation, and, upon treatment with acid, cyclized to cleanly form bicyclic lactone **55** in 68% yield over three steps (Scheme 5.18). No purification was needed until after the acid-catalyzed cascade epoxide-opening reaction, and no loss in optical purity was observed as determined by chiral HPLC analysis. Racemic **55** was a crystalline solid, and an X-ray crystal structure was obtained to prove the relative stereochemistry (Figure 5.4). Compound **55** resembles **51** (with a lactone in place of an ether) and is in the opposite absolute configuration relative to the initially targeted intermediate **42**. The original approach to 5-*epi*-citreoviral involved a base-induced cyclization, which would have led to the (–)-enantiomer. On the other hand compound **55** would lead to (+)-5-*epi*-citreoviral. Because both enantiomers of the chiral diamine used to make catalyst **23** are commercially available, both enantiomers of **55** should be accessible using the approach described here.



Scheme 5.18. Synthesis of lactone **55** using an acid-catalyzed cascade epoxide-opening reaction.

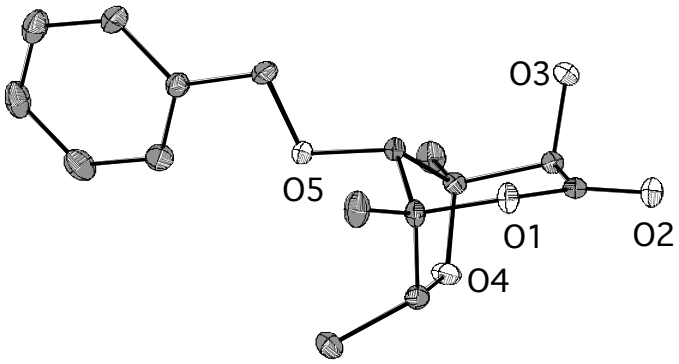
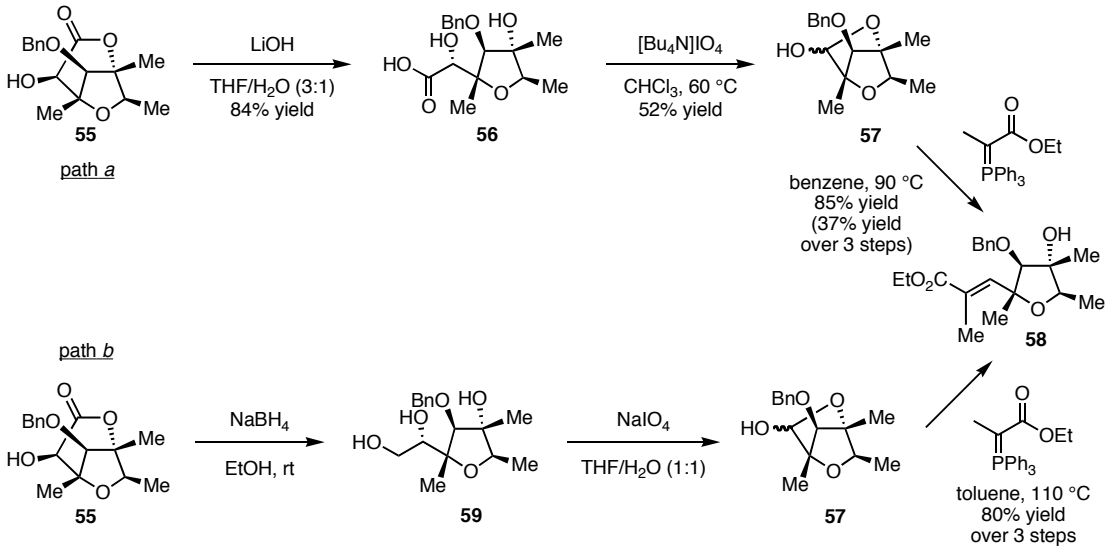


Figure 5.4. Structure of **55** with displacement ellipsoids drawn at 50% probability.

Lactone **55** contains the desired substituted tetrahydrofuran ring and can be further functionalized in a straightforward manner. The first route developed to unsaturated ester **58** is illustrated in path *a* of Scheme 5.19. The lactone was hydrolyzed with aqueous LiOH, and the resulting α-hydroxy acid was oxidatively cleaved with tetrabutylammonium periodate.[27] Treatment of **57** (which was a mixture of the hydroxy aldehyde and both diastereomers of the lactol in $CDCl_3$ and DMSO-d_6) with a stabilized

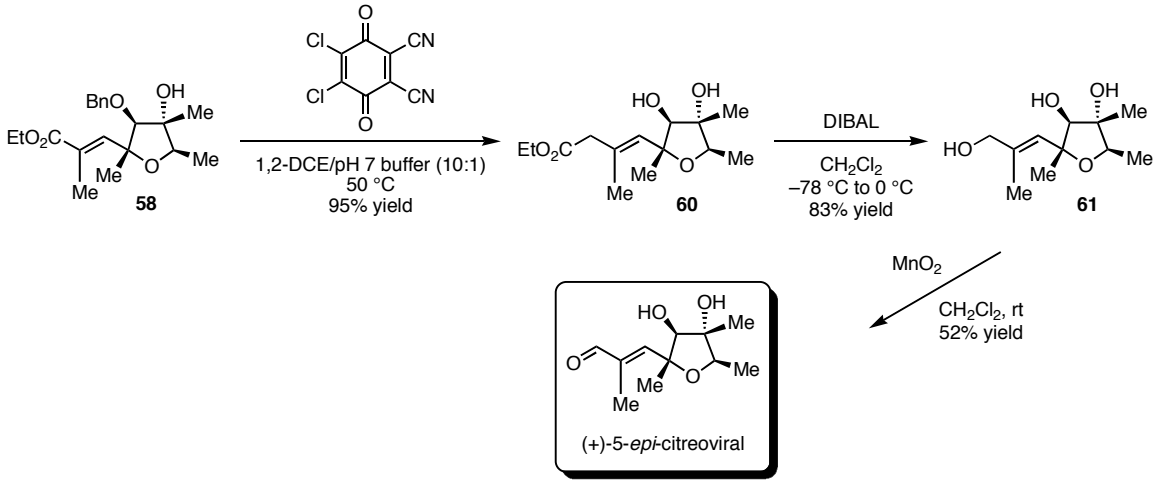
phosphorus ylide gave compound **58** in 37% yield over three steps. The oxidative cleavage reaction proceeded in 52% yield and column chromatography was needed after this step. An alternative route was developed (Scheme 5.19, path *b*) where unsaturated ester **58** was isolated as a 12:1 *E*/*Z* mixture in 80% yield over three steps with no chromatography until after the Wittig reaction.



Scheme 5.19. Original (path *a*) and improved (path *b*) synthesis of unsaturated ester **58**.

Compound **58** is a late-stage intermediate in the synthesis of (±)-5-*epi*-citreoviral by the Woerpel group,[18] and the final three steps in the synthesis described here are the same as those used by Woerpel (Scheme 5.20). The benzyl ether was oxidatively deprotected with DDQ, and the ethyl ester was reduced to an allylic alcohol using diisobutylaluminum hydride. Finally, chemoselective oxidation of the primary allylic alcohol was achieved using activated manganese dioxide, and (+)-5-*epi*-citreoviral ((+)-**2**) was isolated in 2.4% yield over 17 steps (average of 80% yield per step). The ^{1}H and ^{13}C NMR spectra of the (+)-5-*epi*-citreoviral synthesized here match the spectra obtained by Woerpel.[18] Attempts to improve the yield of the final step using other procedures known to selectively oxidize a primary allylic alcohol over a secondary alcohol were not

successful.[28] Additionally, the final oxidation with MnO_2 only yielded (+)-5-*epi*-citreoviral when it was carried out in dry solvent under an atmosphere of argon.



Scheme 5.20. Completion of (+)-5-*epi*-citreoviral.

Conclusion

The total synthesis of (+)-5-*epi*-citreoviral has been accomplished using ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM). Low catalyst loadings (<1 mol %), good yields, and high enantiomeric excesses made ARCM practical for use as a very early synthetic step. All of the stereocenters in the final product were set from the one chiral center generated in the ARCM step. In addition to ARCM, other key steps were the substrate-directed bis-epoxidation reaction, which set four chiral centers in one step, and the acid-catalyzed cascade epoxide-opening reaction, which generated the substituted tetrahydrofuran found in (+)-5-*epi*-citreoviral. A direct route to 2,6-dioxabicyclo[3.2.1]octane ring systems from hydroxy bis-epoxides using both acidic and basic conditions was also discovered. This synthesis illustrates how simple

compounds made using olefin metathesis can be readily transformed into biologically interesting molecules.

Experimental

General Information. NMR spectra were recorded on an Oxford 300 MHz NMR spectrometer running Varian VNMR software. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS) with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a wavelength of 589 nm. The concentration "c" has units of g/100 mL (or 10 mg/mL) unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm thickness) with a fluorescent indicator. Visualization was performed with standard potassium permanganate stain (10 g $KMnO_4$, 20 g Na_2CO_3, 1 L water), standard *p*-anisaldehyde stain (23 mL *p*-anisaldehyde in 500 mL 95% EtOH, cooled to 0 °C, added 9.4 mL cold glacial AcOH and 31.3 mL conc. H_2SO_4, diluted to 1 L with 95% EtOH) or UV light. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh). All enantiomeric purities were determined by chiral GC (Chiraldex G-TA) or chiral SFC (supercritical CO_2, ADH column, 214 nm UV detection) and were compared to racemic samples. All glassware was flame dried, and reactions were done under an atmosphere of argon unless otherwise noted. All organic solvents were dried by passage through solvent purification columns containing activated alumina and activated

copper (for solvents with no heteroatoms). All commercial chemicals were used as obtained.

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (22). Titanocene dichloride (444 mg, 1.78 mmol) was added to a solution of 2-butyne (5.6 mL, 71 mmol) and isobutylmagnesium bromide (2.0 M in diethyl ether, 33 mL, 66 mmol) in 60 mL Et_2O, and the solution stirred at rt for 1 h. *Trans*-2-methyl-2-butenal (5.7 mL, 59 mmol) in 30 mL Et_2O was added slowly, and the mixture stirred at rt for 3 h. It was quenched with saturated aqueous NH_4Cl (100 mL), filtered through a pad of Celite, and the organic layer was removed from the filtrate. The aqueous layer was extracted with ether (3 × 75 mL), and the organic layers were combined, washed with brine, dried over $MgSO_4$, and evaporated to a brown oil. The oil was purified by flash chromatography (10% ethyl acetate in hexanes) to a yellow oil, which was distilled (Kugelrohr, 1 torr, 120 °C) to afford 7.20 g (86% yield) of **22** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56 (qquint, J = 6.6, 1.4 Hz, 2H), 4.34 (s, 1H), 1.63 (dt, J = 6.9, 1.1 Hz, 6H), 1.47 (t, J = 1.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.1, 120.4, 81.8, 13.3, 12.1. HRMS (EI) *m*/*z* calc. for $C_9H_{16}O$ (M^+) 140.1201, found 140.1203.

Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)dimethylsilane (20).

Allylchlorodimethylsilane (1.1 mL, 0.98 g, 7.5 mmol) was added to a solution of **22** (1.0 g, 7.1 mmol), triethylamine (1.2 mL, 0.87 g, 8.6 mmol), and *N*,*N*-dimethylaminopyridine (44 mg, 0.4 mmol) in 30 mL CH_2Cl_2 at rt. After 5 h the reaction was quenched with 50 mL water, the organic layer was removed, and the aqueous layer

was extracted with ether (3 × 50 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4, and evaporated to an oil. The oil was redissolved in hexanes and was filtered through a pad of neutral alumina. The filtrate was condensed to give 1.30 g (76% yield) **20** as a colorless oil. Attempts to purify **20** by silica gel chromatography resulted in inconsistent yields and varying levels of purity due to product decomposition. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.70–5.85 (m, 1H), 5.52 (qquint, J = 6.9, 1.4 Hz, 2H), 4.80–4.90 (m, 2H), 4.30 (s, 1H), 1.61 (dt, J = 6.9, 1.1 Hz, 6H), 1.58–1.63 (m, 2H), 1.43 (t, J = 1.1 Hz, 6H), 0.08 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.4, 134.8, 119.9, 113.5, 82.4, 25.1, 13.3, 12.0, –1.9. HRMS (EI) *m/z* calc. for $C_{14}H_{26}OSi$ (M^+) 238.1753, found 238.1752.

(*S*,*E*)-6-(But-2-en-2-yl)-2,2,5-trimethyl-3,6-dihydro-2*H*-1,2-oxasiline (19). Triene **20** (0.95 g, 4.0 mmol) was added to a solution of **23** (35 mg, 0.032 mmol) in CH_2Cl_2 (72 mL), and the reaction stirred at 40 °C for 2 h. The solvent was evaporated, and the remaining residue was purified by flash chromatography (3% ethyl acetate in hexanes) to afford 0.70 g (89% yield) of **19** as a pale yellow oil in 92% *ee* (chiral GC, Chiraldex G-TA column, 60 °C for 60 min, 1 mL/min, 28.6 (minor) and 30.0 (major) min retention times for the two enantiomers). $[\alpha]_D^{25}$ = +195.4 ($CHCl_3$, *c* = 0.96). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.69 (dquint, J = 7.7, 1.4 Hz, 1H), 5.49 (q, J = 6.6 Hz, 1H), 4.54 (s, 1H), 1.63 (dd, J = 6.6, 1.1 Hz, 3H), 1.54 (t, J = 1.1 Hz, 3H), 1.51 (s, 3H), 1.29–1.39 (m, 1H), 1.12–1.21 (m, 1H), 0.19 (s, 3H), 0.13 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 136.9, 136.0, 122.9, 120.4, 83.4, 22.0, 13.5, 12.5, 10.7, 0.3, –0.6. HRMS (EI) *m/z* calc. for $C_{11}H_{20}OSi$ (M^+) 196.1284, found 196.1281.

(*S*,2*Z*,5*E*)-3,5-Dimethylhepta-2,5-diene-1,4-diol (24). KF (1.02 g, 17.6 mmol), $KHCO_3$ (0.88 g, 8.8 mmol), and 30% H_2O_2 (4.0 mL, 4.0 g, 35 mmol) were added to a solution of **19** (0.69 g, 3.5 mmol) in THF (35 mL) and MeOH (35 mL), and the reaction mixture stirred at rt for 12 h. The solvents were evaporated until only a small volume remained (~10 mL). Water (25 mL) was added, and the solution was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to an oil. Purification by flash chromatography (1:1 ethyl acetate/hexanes) afforded 0.40 g (72% yield, 64% yield over two steps) of **24** as a thick, colorless oil. $[\alpha]_D^{25.3}$ = –54.7 (c = 0.93). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.56–5.64 (m, 2H), 4.83 (s, 1H), 4.27 (dd, J = 12.5, 7.7 Hz, 1H), 4.15 (dd, J = 12.5, 6.3 Hz, 1H), 2.32 (br s, 2H), 1.62–1.65 (m, 3H), 1.63 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 140.1, 135.4, 126.9, 119.7, 74.9, 58.4, 19.0, 13.3, 13.0. HRMS (EI) *m*/*z* calc. for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1145.

(*S*,2*Z*,5*E*)-1-(*Tert*-butyldiphenylsilyloxy)-3,5-dimethylhepta-2,5-dien-4-ol (25). A solution of N,N-dimethylaminopyridine (DMAP) (16 mg, 0.13 mmol) and **24** (0.40 g, 2.5 mmol) in 25 mL CH_2Cl_2 was cooled to 0 °C. Triethylamine (0.53 mL, 0.38 g, 3.8 mmol) was added to the reaction solution followed by a slow addition of *t*-butyldiphenylsilyl chloride (0.73 mL, 0.77 g, 2.8 mmol) over 3 minutes. After 5 minutes at 0 °C, the solution was allowed to warm to rt and continued stirring for 5.5 h. The solution was quenched with 40 mL of water and was extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated

to a pale yellow oil. Purification by flash chromatography (10% ethyl acetate in hexanes) afforded 0.86 g of **25** as a colorless oil contaminated with a small amount (~13%) of *t*-butyldiphenylsilanol (singlet at 1.08 ppm in the ^{1}H NMR spectrum). $[\alpha]_D^{26.2} = -38.9$ (c = 1.25). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.67–7.73 (m, 4H), 7.36–7.46 (m, 6H), 5.48–5.59 (m, 2H), 4.60 (br s, 1H), 4.33 (ddd, J = 12.8, 7.1, 0.8 Hz, 1H), 4.25 (ddd, J = 12.9, 6.0, 1.1 Hz, 1H), 1.69 (d, J = 3.3 Hz, 1H), 1.60 (d, J = 1.4 Hz, 3H), 1.58–1.59 (m, 3H), 1.44 (s, 3H), 1.05 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.89, 135.79, 135.00, 133.81, 129.90, 129.87, 127.93, 127.89, 127.84, 127.47, 119.15, 74.49, 60.23, 26.99, 19.33, 18.51, 13.21, 13.08. HRMS (FAB) *m/z* calc. for $C_{25}H_{33}O_2Si$ ($M^+ - H$) 393.2250, found 393.2280.

(*S*)-((2*R*,3*S*)-3-((*Tert*-butyldiphenylsilyloxy)methyl)-2-methyloxiran-2-yl)((2*R*,3*R*)-2,3-dimethyloxiran-2-yl)methanol (26). To a solution/suspension of **25** (0.86 g, 2.2 mmol) and $NaHCO_3$ (0.92 g, 11 mmol) in 22 mL of CH_2Cl_2 at 0 °C was added MCPBA (71.7 wt %, 2.10 g, 8.72 mmol). After stirring at 4 °C for 13 h, the mixture was diluted with CH_2Cl_2 (40 mL) and filtered through Celite. A solution of saturated aqueous Na_2CO_3 was added to the filtrate, and it was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$, dried over Na_2SO_4, and evaporated to a pale yellow oil. Purification by flash chromatography (20% ethyl acetate in hexanes) afforded 0.48 g (44% yield over two steps) of **26** as a colorless oil. The enantioenriched material was always an oil, but racemic **26** was a solid that was recrystallized from benzene/pentane vapor diffusion. $[\alpha]_D^{25.0} = -20.7$ (c = 0.90). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.67–7.70 (m, 4H), 7.37–7.45 (m, 6H), 3.88 (d, J = 5.5

Hz, 2H), 3.55 (br s, 1H), 3.33 (q, J = 5.8 Hz, 1H), 3.10 (t, J = 5.5 Hz, 1H), 2.20 (d, J = 2.2 Hz, 1H), 1.31 (d, J = 5.8 Hz, 3H), 1.29 (s, 3H), 1.26 (s, 3H), 1.07 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.76, 135.70, 130.10, 128.01, 72.64, 64.69, 61.99, 61.96, 60.82, 54.86, 26.93, 19.35, 17.80, 14.49, 13.39. HRMS (FAB) *m/z* calc. for $C_{25}H_{35}O_4Si$ (M^+ + H) 427.2305, found 427.2299.

(((2*S*,3*S*)-3-((*S*)-Benzyloxy((2*S*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methoxy)(*tert*-butyl)diphenylsilane (37). To a suspension of NaH (95%, 41 mg, 1.7 mmol) in THF (8.4 mL) was added **26** (dried by azeotroping from toluene, 0.36 g, 0.84 mmol) at rt. A small amount of bubbling occurred, and the reaction mixture stirred at 65–70 °C. After 10 minutes, the mixture was allowed to cool to rt and tetrabutylammonium iodide (16 mg, 0.042 mmol) and benzyl bromide (filtered through neutral alumina, 0.30 mL, 0.43 g, 2.5 mmol) were added. After 3 h at 65–70 °C, the mixture was carefully quenched with saturated aqueous NH_4Cl (20 mL) and was extracted with Et_2O (4 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil. Purification by flash chromatography (8% ethyl acetate in hexanes) gave 309 mg (71% yield) of **37** as a colorless oil. $[\alpha]_D^{24.6}$ = –5.9 (c = 0.83). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.68–7.72 (m, 4H), 7.36–7.48 (m, 6H), 7.23–7.34 (m, 5H), 4.69 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.94 (dd, J = 11.8, 4.4 Hz, 1H), 3.73 (dd, J = 11.8, 6.1 Hz, 1H), 3.24 (s, 1H), 3.17 (q, J = 5.5 Hz, 1H), 3.05 (dd, J = 6.1, 4.4 Hz, 1H), 1.24 (d, J = 5.5 Hz, 3H), 1.34 (s, 3H), 1.23 (s, 3H), 1.08 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.80, 135.91, 135.78, 133.49, 133.21, 130.08, 130.06, 128.41, 128.03, 128.00, 127.87, 127.63, 81.07, 73.40, 63.57,

62.48, 62.20, 60.47, 55.89, 27.01, 19.44, 18.54, 14.95, 13.61. HRMS (FAB) *m/z* calc. for $C_{32}H_{41}O_4Si$ ($M^+ + H$) 517.2774, found 517.2764.

((2*S*,3*S*)-3-((*S*)-Benzyloxy((2*S*,3*R*)-2,3-dimethyloxiran-2-yl)methyl)-3-methyloxiran-2-yl)methanol (38). To a solution of **11** (0.30 g, 0.58 mmol) in THF (11mL) was added tetrabutylammonium fluoride (1M in THF, 1.2 mL, 1.2 mmol). After 2.5 h at rt, the solvent was removed by rotary evaporation, and the residue was dissolved in CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL). It was extracted with CH_2Cl_2 (3 × 15 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded 135 mg (83% yield) of **38** as a colorless oil. $[\alpha]_D^{24.4} = -28.0$ (c = 0.86). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.37 (m, 5H), 4.76 (d, J = 12.1 Hz, 1H), 4.56 (d, J = 12.1 Hz, 1H), 3.83 (dd, J = 12.4, 5.0 Hz, 1H), 3.42 (dd, J = 12.4, 8.0 Hz, 1H), 3.12 (br s, 1H), 3.04 (s, 1H), 3.01 (dd, J = 8.0, 5.0 Hz, 1H), 2.87 (q, J = 5.5 Hz, 1H), 1.47 (s, 3H), 1.35 (s, 3H), 1.25 (d, J = 5.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.35, 128.57, 127.95, 127.91, 82.76, 72.47, 62.04, 61.73, 60.78, 60.69, 19.38, 13.77, 13.41. HRMS (FAB) *m/z* calc. for $C_{16}H_{23}O_4$ ($M^+ + H$) 279.1596, found 279.1586.

8-(Benzyloxy)-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-4-ol (45). To a solution of racemic **38** (50 mg, 0.18 mmol) in *t*-BuOH (0.9 mL) was added NaOH (0.5M in H_2O, 0.90 mL, 0.45 mmol). After stirring at 75–80 °C for 6 h, the solution was quenched with saturated aqueous NH_4Cl (1 mL) and was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layeres were dried over Na_2SO_4 and evaporated to an oil. Purification

by flash chromatography (45% ethyl acetate in hexanes) afforded 43.3 mg (87% yield) of **45** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.36 (m, 5H), 4.62 (d, J = 12.3 Hz, 1H), 4.47 (d, J = 12.4, 1H), 4.33 (s, 1H), 4.21 (dd, J = 13.2, 2.5 Hz, J = 1H), 3.85 (d, J = 13.2 Hz, 1H), 3.65 (br s, 1H), 3.49 (q, J = 6.6 Hz, 1H), 2.05 (br s, 1H), 1.43 (s, 3H), 1.23 (s, 3H), 1.00 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 138.30, 128.59, 127.82, 127.40, 89.11, 86.25, 80.17, 76.23, 75.67, 73.46, 72.23, 19.50, 18.56, 17.25. HRMS (FAB) *m/z* calc. for $C_{16}H_{21}O_4$ (M^+ – H) 277.1440, found 277.1432.

(1*R*,4*R*,5*R*,7*R*,8*R*)-8-(Benzyloxy)-4-hydroxy-1,5,7-trimethyl-2,6-dioxabicyclo[3.2.1]octan-3-one (55). To a solution of oxalyl chloride (0.19 mL, 0.28 g, 2.2 mmol) in CH_2Cl_2 (7 mL) at –78 °C was added DMSO (0.25 mL, 0.28 g, 3.6 mmol). After 10 min at –78 °C, **38** (200 mg, 0.72 mmol) was added. After 20 min at –78 °C, triethylamine (0.70 mL, 0.51 g, 5.0 mmol) was added, and the solution stirred at –78 °C for 30 min before warming to rt. After 45 min at rt, the reaction was quenched with water (10 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and evaporated to a yellow oil (**53**), which was used directly in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.38 (d, J = 3.8 Hz, 1H), 7.30–7.39 (m, 5H), 4.64 (d, J = 11.8 Hz, 1H), 4.54 (d, J = 11.8 Hz, 1H), 3.23 (d, J = 3.8 Hz, 1H), 3.15 (s, 1H), 2.81 (q, J = 5.5 Hz, 1H), 1.51 (s, 3H), 1.32 (s, 3H), 1.23 (d, J = 5.5 Hz, 3H). To a solution of crude **53** in *t*-BuOH (5.8 mL) was added 2.9 mL of a pH = 3.8 buffer (NaH_2PO_4, 0.41M in H_2O), 2-methyl-2-butene (0.34 mL, 0.23 g, 3.2 mmol), and $NaClO_2$ (80%, 326 mg, 2.88 mmol). After stirring at rt for 1.5 h, the solution was diluted with pH = 3.8 buffer (10 mL) and was extracted with ethyl acetate (4 × 15

mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil (**54**) that was used directly in the next reaction. To a solution of crude **54** in 8 mL of benzene was added *p*-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol). After 2 h at rt, the solution was diluted with water (10 mL) and was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (30% ethyl acetate in hexanes) afforded 157 mg (68% yield over three steps) of **55** as a colorless oil. The enantioenriched material never crystallized, or even became a solid, but the racemic material was a white solid that was recrystallized from benzene/pentane vapor diffusion. Chiral SFC (supercritical CO_2 with 5% MeOH, ADH column, 214 nm UV detection, 4.78 (minor) and 5.27 (major) min retention times of the enantiomers) showed a 92% *ee*. $[\alpha]_D^{24.9} = -20.0$ (c = 0.96). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.33–7.41 (m, 5H), 4.75 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.6 Hz, 1H), 4.11 (q, J = 6.9 Hz, 1H), 4.07 (s, 1H), 3.81 (s, 1H), 1.46 (s, 3H), 1.45 (s, 3H), 1.27 (d, J = 6.6 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 172.73, 137.41, 128.76, 128.33, 127.96, 91.23, 83.21, 83.17, 82.88, 75.81, 75.16, 18.68, 16.54, 16.08. HRMS (EI) *m*/*z* calc. for $C_{16}H_{20}O_5$ (M^+) 292.1311, found 292.1305.

(*E*)-Ethyl-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (58) through 56 (Scheme 5.19, path *a*). To a solution of racemic **55** (160 mg, 0.55 mmol) in THF (6.8 mL) was added LiOH (0.72M in water, 2.3 mL, 1.6 mmol). After 2.5 h at rt, the solution was diluted with 7 mL of 1N HCl (aqueous) and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (2% acetic acid

in ethyl acetate) afforded 142 mg (84% yield) of **56** as a colorless, sticky oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.36 (m, 5H), 4.71 (d, J = 11.5 Hz, 1H), 4.65 (d, J = 11.5 Hz, 1H), 4.27 (s, 1H), 4.24 (s, 1H), 3.89 (q, J = 6.6 Hz, 1H), 1.27 (s, 3H), 1.24 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H). Tetrabutylammonium periodate (243 mg, 0.56 mmol) was added to a solution of **56** (142 mg, 0.51 mmol) in 3.5 mL of $CHCl_3$. After 12 h at 62 °C, the solution was diluted with saturated aqueous $Na_2S_2O_3$ and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography (40% ethyl acetate in hexanes) afforded 63 mg (52% yield) of **57** as a yellow oil. The ^{1}H NMR spectrum in $CDCl_3$ was unclean and showed no peak corresponding to an aldehyde hydrogen; it is presumably in the lactol form in $CDCl_3$. In DMSO-d_6 an aldehyde peak was present, and the spectrum showed multiple forms of **57** (both diastereomers of the lactol and the aldehyde). ^{1}H NMR (300 MHz, ppm) diagnostic signals: δ 4.70 (s, $CDCl_3$), 3.93 (q, J = 6.9 Hz, $CDCl_3$), 3.46 (s, $CDCl_3$); 9.53 (s, DMSO-d_6). The phosphorus ylide (carbethoxyethylidene)triphenylphosphorane (11 mg, 0.030 mmol) was added to a solution of **57** in benzene (0.3 mL) in a 1 dram vial, which was sealed. After 48 h at 90 °C, the reaction mixture was directly placed on a silica gel column and was purified by flash chromatography (20% ethyl acetate in hexanes) to afford 5.3 mg (85% yield, 37% over three steps) of **58** (12:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 5.32 (d, J = 1.4 Hz, 1H)) as a very pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.28–7.40 (m, 5H), 6.87 (d, J = 1.4 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.89 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 1.94 (d, J = 1.1 Hz, 3H), 1.59 (br s, 1H), 1.32 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (s,

3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 168.68, 148.59, 138.25, 128.64, 127.96, 127.79, 127.62, 92.22, 82.07, 80.57, 77.34, 72.95, 61.00, 21.99, 16.65, 14.47, 13.74, 12.71.

(*E*)-Ethyl-3-((2*R*,3*S*,4*R*,5*R*)-3-(benzyloxy)-4-hydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylate (58) through 59 (Scheme 5.19, path *b*). To a solution of $NaBH_4$ (91 mg, 2.4 mmol) in ethanol (7 mL) was added **55** (140 mg, 0.48 mmol) as a solution in 4 mL of ethanol. After 4.5 h at rt, the solvent was removed by rotary evaporation, and the remaining residue was dissolved/suspended in ethyl acetate and quenched with 1N aqueous HCl until the pH was <2. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (4 × 15 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a sticky oil (**59**) that was used directly in the next step. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.27–7.37 (m, 5H), 4.78 (d, J = 11.8 Hz, 1H), 4.61 (d, J = 11.8 Hz, 1H), 4.07 (s, 1H), 3.88 (q, J = 6.6 Hz, 1H), 3.77–3.82 (m, 1H), 3.56–3.64 (m, 2H), 1.26 (s, 3H), 1.15 (s, 3H), 1.14 (d, J = 6.6 Hz, 3H). To a solution of crude **59** in THF (3 mL) was slowly added $NaIO_4$ (113 mg, 0.53 mmol) as a solution in 3 mL of water. After 1 h at rt, the reaction solution was diluted with water (10 mL) and extracted with ethyl acetate (5 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to a pale yellow oil (**57**) that was used directly in the next step. The ^{1}H NMR spectrum in $CDCl_3$ was unclean and showed no peak corresponding to an aldehyde hydrogen; it is presumably in the lactol form in $CDCl_3$. In DMSO-d_6 an aldehyde peak was present, and the spectrum showed multiple forms of **57** (both diastereomers of the lactol and the aldehyde). ^{1}H NMR (300 MHz,

ppm) diagnostic signals: δ 4.70 (s, $CDCl_3$), 3.93 (q, J = 6.9 Hz, $CDCl_3$), 3.46 (s, $CDCl_3$); 9.53 (s, DMSO-d_6). The phosphorus ylide (carbethoxyethylidene)triphenylphosphorane (0.52 g, 1.4 mmol) was added to a solution of crude **57** in toluene (5 mL). After 18 h at 110 °C, the solvent was removed by rotary evaporation. The remaining residue was purified by flash chromatography (25% ethyl acetate in hexanes) to afford 136 mg (80% over three steps) of **58** (12:1 *E*/*Z*, *Z* isomer has a peak in the ^{1}H NMR spectrum ($CDCl_3$) at δ 5.32 (d, J = 1.4 Hz, 1H)) as a very pale yellow oil. $[\alpha]_D^{25.3}$ = +48.3 (c = 0.99). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.28–7.40 (m, 5H), 6.87 (d, J = 1.4 Hz, 1H), 4.83 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.8 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.89 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 1.94 (d, J = 1.1 Hz, 3H), 1.59 (br s, 1H), 1.32 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.24 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 168.68, 148.59, 138.25, 128.64, 127.96, 127.79, 127.62, 92.22, 82.07, 80.57, 77.34, 72.95, 61.00, 21.99, 16.65, 14.47, 13.74, 12.71. HRMS (FAB) *m*/*z* calc. for $C_{20}H_{29}O_5$ (M^+ + H) 349.2015, found 349.2026.

(*E*)-Ethyl 4-((2*R*,3*S*,4*S*,5*R*)-3,4-dihydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-3-methylbut-3-enoate (60). To a solution of **58** (66 mg, 0.19 mmol) in 1,2-dichloroethane (3.1 mL) and pH 7 buffer (0.31 mL) was added DDQ. After 13 h at 50 °C, saturated aqueous $NaHCO_3$ (10 mL) and ethyl acetate (10 mL) were added, and the mixture was filtered through Celite. The filtrate was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were dried over Na_2SO_4 and evaporated to an brown oil. Purification by flash chromatography (55% ethyl acetate in hexanes) afforded 47 mg (95% yield) of **60** as a very pale purple solid (mp = 94–96 °C). $[\alpha]_D^{24.6}$ = +20.2 (c =

0.86). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 6.87 (d, J = 1.7 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 4.06 (s, 1H), 3.68 (q, J = 6.3 Hz, 1H), 2.92 (br s, 2H), 1.97 (d, J = 1.4 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.27 (s, 3H), 1.16 (s, 3H), 1.15 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 169.13, 148.50, 127.75, 85.59, 82.34, 80.45, 61.22, 21.37, 16.32, 14.40, 14.34, 12.87. HRMS (EI) *m/z* calc. for $C_{13}H_{22}O_5$ (M^+) 258.1467, found 258.1463.

(2*R*,3*S*,4*S*,5*R*)-2-((*E*)-3-Hydroxy-2-methylprop-1-enyl)-2,4,5-trimethyltetrahydrofuran-3,4-diol (61). A solution of diisobutylaluminum hydride (1.5M in toluene, 0.93 mL, 1.4 mmol) was added to a solution of **60** (45 mg, 0.17 mmol) in CH_2Cl_2 (2.3 mL) at –78 °C. The solution became yellow. After 1.5 h at –78 °C, the solution was allowed to warm to 0 °C. After 1 h at 0 °C, the solution was carefully quenched with a saturated aqueous solution of potassium sodium tartrate (Rochelle's salt, 5 mL). Et_2O (5 mL) was added to the solution, and it stirred vigorously at rt for 12 h. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (7 × 10 mL). The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Purification by flash chromatography afforded 31 mg (83% yield) of **61** as a sticky, colorless oil. $[\alpha]_D^{24.9}$ = +28.4 (c = 1.09). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 5.65 (d, J = 1.4 Hz, 1H), 4.04 (s, 1H), 3.96 (s, 2H), 3.74 (q, J = 6.3 Hz, 1H), 2.58 (br s, 3H), 1.80 (s, 3H), 1.27 (s, 3H), 1.18 (s, 3H), 1.17 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 135.31, 132.58, 86.51, 82.47, 81.05, 77.86, 68.59, 22.43, 16.53, 14.78, 14.28. HRMS (CI) *m/z* calc. for $C_{11}H_{21}O_4$ (M^+ + H) 217.1440, found 217.1443.

(*E*)-3-((2*R*,3*S*,4*S*,5*R*)-3,4-Dihydroxy-2,4,5-trimethyltetrahydrofuran-2-yl)-2-methylacrylaldehyde ((+)-5-*epi*-citreoviral, (+)-2). To a solution of **61** (17 mg, 0.080 mmol) in 2.7 mL of CH_2Cl_2 was added activated MnO_2 (85%, 81 mg, 0.80 mmol), and the mixture stirred vigorously. After 2 h at rt, the mixture was filtered through Celite, and the Celite was washed with CH_2Cl_2 (3 × 10 mL) and ethyl acetate (3 × 10 mL). The filtrate was evaporated to an oil, which was purified by flash chromatography (60% ethyl acetate in hexanes) to afford 8.7 mg (52% yield) of (+)-**2** as a colorless oil. $[\alpha]_D^{25.0}$ = +13.2 (c = 1.74). ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.37 (s, 1H), 6.63 (d, J = 1.4 Hz, 1H), 4.11 (s, 1H), 3.74 (q, J = 6.3 Hz, 1H), 2.02 (br s, 2H), 1.89 (d, J = 1.4 Hz, 3H), 1.35 (s, 3H), 1.23 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm): δ 195.82, 160.64, 138.17, 85.40, 82.69, 80.53, 78.41, 21.20, 16.78, 14.70, 9.66. HRMS (EI) *m*/*z* calc. for $C_{11}H_{18}O_4$ (M^+) 214.1205, found 214.1196.

X-ray Crystallographic Data

Complex	**26**	**55**
Empirical formula	$C_{25}H_{34}O_4Si$	$C_{16}H_{20}O_5$
Formula weight	426.61	292.32
Crystal habit	Tabular	Fragment
Crystal size	0.40 × 0.31 × 0.19 mm^3	0.42 × 0.41 × 0.30 mm^3
Crystal color	Colorless	Colorless
Diffractometer	Bruker SMART 1000	Bruker SMART 1000
Wavelength	0.71073 Å MoKα	0.71073 Å MoKα
Temperature	100(2) K	100(2) K
Unit cell dimensions	a = 34.970(2) Å	a = 8.3224(3) Å
	b = 9.6943(5) Å	b = 9.9930(4) Å
	c =14.8230(9) Å	c =17.8237(7) Å
	β = 110.1100(10)°	β = 97.0980(10)°
Volume	4718.7(5) $Å^3$	1470.96(10) $Å^3$
Z	8	4
Crystal system	Monoclinic	Monoclinic
Space group	Cc	$P2_1/c$
Density (calculated)	1.201 Mg/m^3	1.320 Mg/m^3
Theta range	2.19 to 32.74°	2.30 to 42.65°
h min, max	–49, 53	–13, 15
k min, max	–14, 14	–18, 15
l min, max	–20, 19	–33, 32
Reflections collected	37444	28796
Independent reflections	13856	9804
R_{int}	0.0595	0.0680
GOF on F^2	2.147	1.384
Final R indicies [I>2σ(I)]	0.0657	0.0507
Final weighted R [F_o^2]	0.1272	0.0892

References

[1] Seebach, D.; Weidmann, B.; Wilder, L. In *Modern Synthetic Methods 1983*; Scheffold, R., Ed.; Otto Salle Verlag: Frankfurt, 1983; p 323.

[2] Shizuri, Y.; Nishiyama, S.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1984**, *25*, 4771–4774.

[3] Nishiyama, S.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 231–234.

[4] Sakabe, N.; Goto, T.; Hirata, Y. *Tetrahedron* **1977**, *33*, 3077–3081.

[5] (a) Boyer, P. D.; Chance, B.; Ernster, L.; Mitchell, P.; Racker, E.; Slater, E. C. *Annu. Rev. Biochem.* **1977**, *46*, 955–1026. (b) Muller, J. L. M.; Rosing, J. Slater, E. C. *Biochim.*

Biophys. Acta **1977**, *462*, 422–437. (c) Gause, E. M.; Buck, M. A.; Douglas, M. G. *J. Biol. Chem.* **1981**, *256*, 557–559.

[6] Mulheirn, L. J.; Beechey, R. B.; Leworthy, D. P.; Osselton, M. D. *J. Chem. Soc., Chem. Commun.* **1974**, *21*, 874–876.

[7] (a) Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem Commun.* **1985**, *22*, 1531–1532. (b) de Jesus, A. E.; Steyn, P. S.; Vleggaar, R. *J. Chem. Soc., Chem Commun.* **1985**, *22*, 1633–1635.

[8] Bowden, M. C.; Patel, P.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1947–1950.

[9] Lai, S.; Matsunaga, K.; Shizuri, Y.; Yamamura, S. *Tetrahedron Lett.* **1990**, *31*, 5503–5506.

[10] Ebenezer, W.; Pattenden, G. *Tetrahedron Lett.* **1992**, *33*, 4053–4056.

[11] (a) ref. 8. (b) Forbes, J. E.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1959–1966. (c) Forbes, J. E.; Bowden, M. C.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, *8*, 1967–1973. (d) ref. 10.

[12] Murata, Y.; Kamino, T.; Aoki, T.; Hosokawa, S.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3175–3177, and references therein.

[13] (a) Hatakeyama, S.; Matsui, Y.; Suzuki, M.; Sakurai, K.; Takano, S. *Tetrahedron Lett.* **1985**, *26*, 6485–6488. (b) ref. 12.

[14] (a) Whang, K.; Venkataraman, H.; Kim, Y. G.; Cha, J. K. *J. Org. Chem.* **1991**, *56*, 7174–7177. (b) Mulzer, J.; Bilow, J.; Wille, G. *J. Prakt. Chem.* **2000**, *342*, 773–778.

[15] (a) ref. 3. (b) Suh, H.; Wilcox, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 470–481. (c) Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223–226.

[16] Trost, B. M.; Lynch, J. K.; Angle, S. R. *Tetrahedron Lett.* **1987**, *28*, 375–378.

[17] Williams, D. R.; White, F. H. *J. Org. Chem.* **1987**, *52*, 5067–5079.

[18] Peng, Z.-H.; Woerpel, K. A. *Org. Lett.* **2002**, *4*, 2945–2948.

[19] (a) Garner, C. M.; Prince, M. E. *Tetrahedron Lett.* **1994**, *35*, 2463–2464. (b) Sato, F.; Ishikawa, H.; Sato, M. *Tetrahedron Lett.* **1981**, *22*, 85–88.

[20] Tamao, K.; Ishida, N.; Ito, Y.; Kumada, M. *Org. Synth.* **1990**, *69*, 96–102.

[21] Yao, Q. *Org. Lett.* **2001**, *3*, 2069–2072.

[22] For acyclic stereocontrol in allylic alcohol epoxidation, see (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta*, **1979**, *12*, 63–74. (b) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733–4736. (c) Tomioka, H.; Suzuki, T.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1982**, *23*, 3387–3390.

[23] Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819–3822.

[24] Formation of the 2,6-dioxabicyclo[3.2.1]octane core in nature in one step from a cascade epoxide opening sequence has been proposed. See references 11b and 11c.

[25] (a) Nishiyama, S.; Shizuri, Y.; Imai, D.; Yamamura, S. *Tetrahedron Lett.* **1985**, *26*, 3243–3246. (b) Bowden, M. C.; Pattenden, G. *Tetrahedron Lett.* **1985**, *26*, 4797–4800. (c) Nishiyama, S.; Toshima, H.; Yamamura, S. *Chem. Lett.* **1986**, 1973–1976. (d) Nishiyama, S.; Toshima, H.; Kanai, H.; Yamamura, S. *Tetrahedron* **1988**, *44*, 6315–6324.

[26] Intermolecular trapping of 2,3-epoxy alcohols: (a) Katsuki, T.; Lee, A. W. M.; Ma, P.; Martin, V. S.; Masamune, S.; Sharpless, K. B.; Tuddenham, D.; Walker, F. J. *J. Org. Chem.* **1982**, *47*, 1378–1380. (b) Behrens, C. H.; Ko, S. Y.; Sharpless, K. B.; Walker, F. J. *J. Org. Chem.* **1985**, *50*, 5687–5696. (c) Behrens, C. H.; Sharpless, K. B. *Aldrichimica Acta*. **1983**, *16*, 67–79.

[27] Santaniello, E.; Manzocchi, A.; Farachi, C. *Synthesis*, **1980**, 563–565.

[28] Tempo oxidation: (a) Einhorn, J.; Einhorn, C.; Ratajczak, F.; Pierre, J.-L. *J. Org. Chem.* **1996**, *61*, 7452–7454. For examples of $BaMnO_4$ in the synthesis of citreoviral, see (b) ref. 12. (c) ref. 15c.

Appendix 1
Insight into Tetrasubstituted Olefin Synthesis

Although olefin metathesis has found widespread use in organic synthesis,[1] the generation of tri- and tetrasubstituted alkenes with ruthenium alkylidene catalysts still remains a challenging problem. Catalysts **1** and **2** (Figure A1.1) have been used to form trisubstituted olefins through ring-closing metathesis[2] and cross-metathesis.[3] However, when macrocycles or acyclic olefins (via cross-metathesis) are being synthesized, substitution larger than methyl on the reacting olefin is not tolerated well, and the yields for these processes are generally low (Scheme A1.1). Tetrasubstituted alkenes are even more challenging to make, and even the highly active catalyst **2** does not afford **4** in high yield.

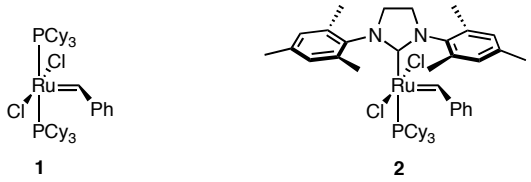
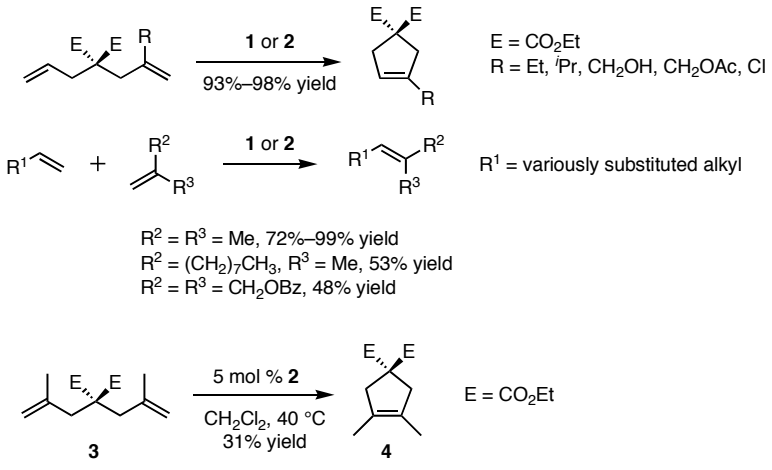


Figure A1.1. Ruthenium olefin metathesis catalysts.



Scheme A1.1. Examples of ring-closing and cross-metathesis to form tri- and tetrasubstituted olefins.

During a routine catalyst screening of an asymmetric ring-closing metathesis (ARCM) substrate (**9**), insight into why catalyst **2** and other similar catalysts containing *N*-heterocyclic carbenes (NHCs) do not efficiently afford tetrasubstituted olefins was discovered. When **9** was treated with **2**, the expected seven-membered ring **10** was exclusively generated and was isolated in 94% yield (Figure A1.2). On the other hand, the reaction of **9** with chiral catalyst **5** afforded a 7:3 mixture of **10** and the five-membered ring, tetrasubstituted olefin **11**. Chiral catalysts **6**, **7**, and **8**, which contain bulky meta substituents on the *N*-bound aryl rings, also formed a mixture of **10** and **11**.

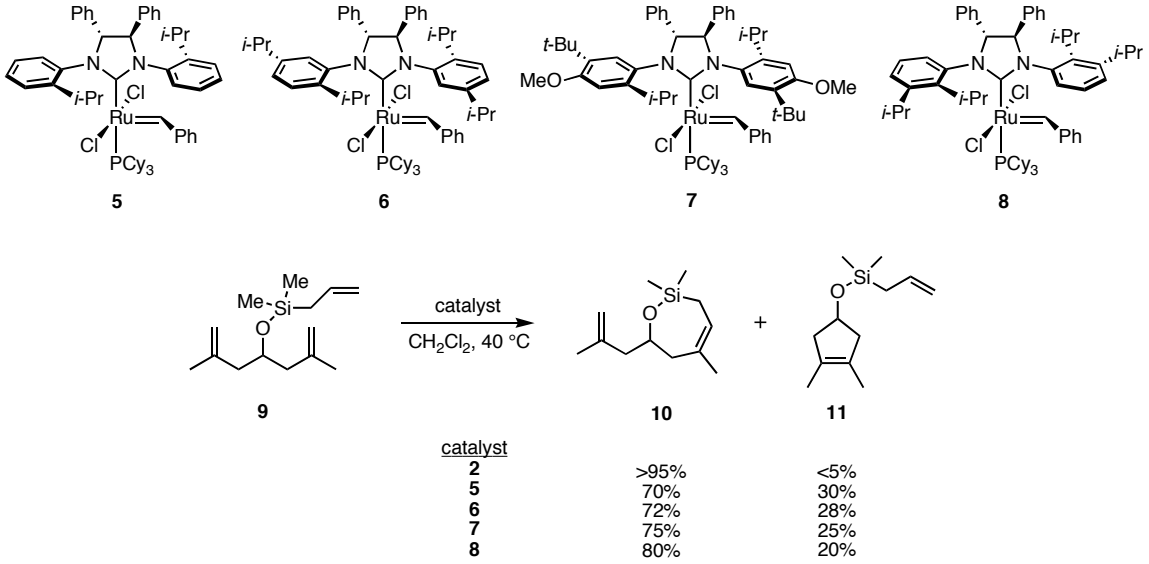
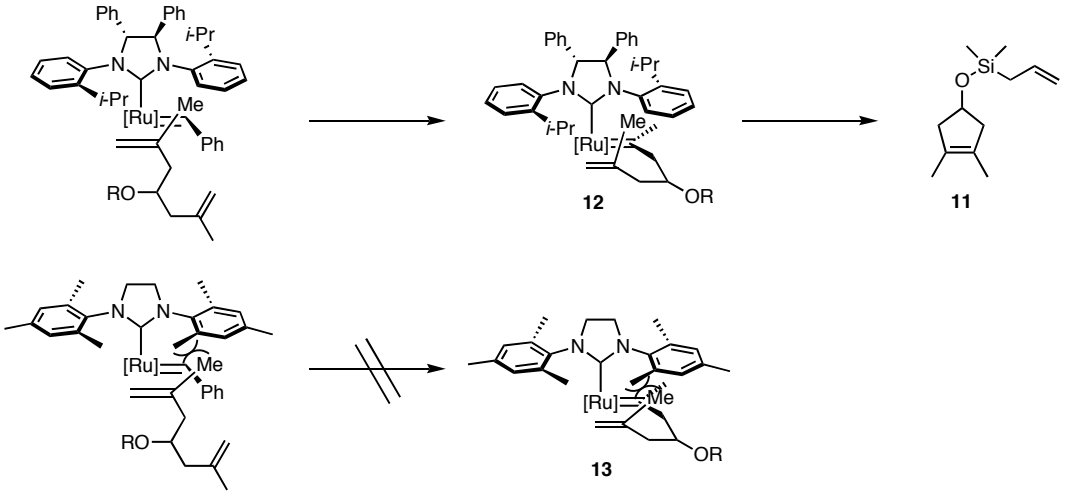


Figure A1.2. Competitive formation of a tetrasubstituted alkene using chiral ruthenium catalysts.

This result was very interesting because no **11** could be detected in the reaction with the achiral catalyst **2**. For some reason, the chiral catalysts were able to generate a tetrasubstituted alkene where the achiral variant could not. The NHC rings are saturated, and the *N*-bound aryl rings are almost orthogonal to the plane of the NHC in the chiral catalysts, so electronically, they are presumably similar to **2**. From a steric point of view, all of the chiral catalysts have only two ortho substituents, but the achiral catalyst **2** has

methyl groups in all four ortho positions. Therefore, the chiral catalysts may be less crowded at the ruthenium center relative to the achiral variant with complete ortho substitution. It was proposed that the lack of ortho substitution allowed a 1,1-disubstituted olefin to react with the catalyst, affording a disubstituted ruthenium alkylidene (**12**) (Scheme A1.2). The achiral catalyst with mesityl rings would have a methyl/methyl interaction, disfavoring the formation of **13**.



Scheme A1.2. Differences in steric environments of chiral and achiral catalysts.

If it really was the lack of ortho substitution allowing **12**, and therefore **11**, to form, it would be expected that other catalysts with no ortho substituents would also generate tetrasubstituted alkenes. A few catalysts have been synthesized where the *N*-bound aryl rings have only C–H bonds or C–F bonds in the ortho positions, and they are able to catalyze the ring closing of **3** to **4** much more efficiently than **2**.[4] Although more optimization is needed, these new complexes lacking ortho substitution could lead to the development of olefin metathesis catalysts that reliably generate tri- and tetrasubstituted alkenes.

References

[1] *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Volume 2.

[2] (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310-7318. (b) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953-956. (c) Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505-2507. (d) Han, S.-Y.; Chang, S. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 2.2. (e) Fürstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem. Eur. J.* **2001**, *7*, 3236-3253.

[3] (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751-1753. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783-3784. (c) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939-1942.

[4] Berlin, J. M.; Ritter, T.; Campbell, K. California Institute of Technology, 2006, unpublished results.

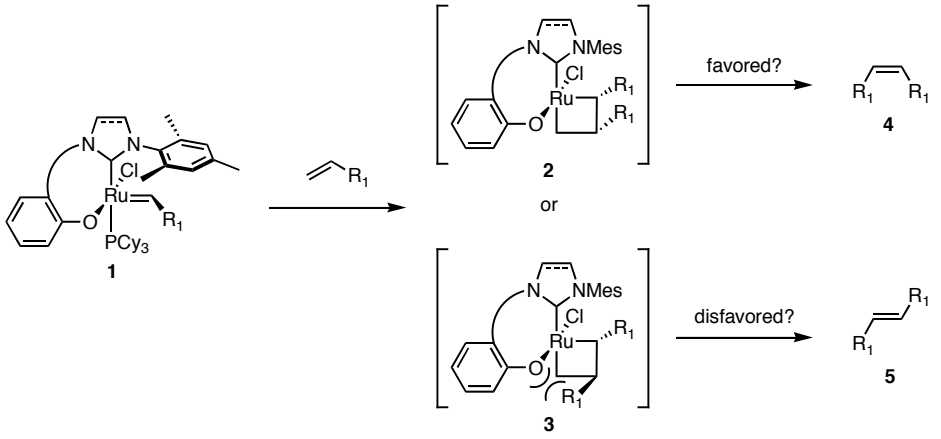
Appendix 2
Efforts toward a Ruthenium Olefin Metathesis Catalyst Bearing an *N*-Heterocyclic Carbene/Phenol Bidentate Ligand

Introduction

Two alkene isomers can be formed in an olefin metathesis reaction: the *E*-isomer or the *Z*-isomer. Rings that are five, six, or seven membered contain a *Z*-isomer, so there are no stereoselectivity issues in those ring-closing metathesis (RCM) reactions. On the other hand, macrocyclic RCM, cross-metathesis (CM), and ring-opening cross-metathesis (ROCM) can afford either isomer. All of the highly active ruthenium catalysts that have been developed to date favor the formation of *E*-olefins over *Z*-olefins in CM,[1] macrocyclic RCM,[2] and low-strain ROCM reactions,[3] most likely due to the thermodynamic nature of metathesis. In some cases, the *E*-isomer is not strongly preferred over the *Z*-isomer, but *E*/*Z* ratios do not typically drop below 1:1.[4] In general, CM reactions between monosubstituted, terminal olefins afford alkenes with *E*/*Z* ratios ranging from 2:1 to >20:1 depending upon the catalyst structure and the alkene sterics and electronics. There is almost no selectivity (1:1–2:1 *E*/*Z*) in ROCM reactions of strained rings.[5]

Because known ruthenium alkylidenes typically generate products enriched in *E*-olefins, catalysts that are selective for *Z*-olefins would be complimentary to the existing technology. In order to make a *Z*-olefin using metathesis, a ligand on the catalyst would have to interact with the metallacyclobutane and force both substituents on the ring to be syn to one another. At the time the work described below began, it was assumed that the incoming olefin bound trans to the *N*-heterocyclic carbene (NHC) ligand, and this has

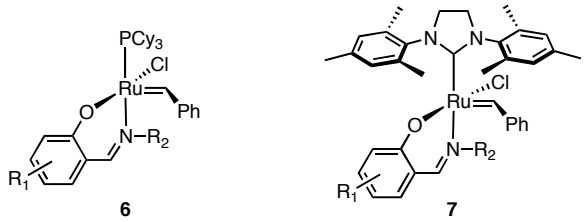
since been reinforced.[6] Based on this hypothesis, a bidentate NHC/phenol ligand structure was proposed (**1**) (Scheme A2.1). This type of ligand would desymmetrize the ruthenium center and could force the substituents on the metallacyclobutane to be syn (**2**).



Scheme A2.1. Proposed *Z*-selective catalyst structure and metallacycle intermediate.

There were a few examples of ruthenium catalysts bearing L,X-type bidentate ligands when this work began. Both classes of compounds had Schiff bases bound to ruthenium: one class had a phosphine ligand,[7] and the other had an NHC ligand[8] (Figure A2.1). None of the complexes in either series were highly active olefin metathesis catalysts; they formed 5-membered rings at elevated temperatures, and they were much less active in CM and macrocyclic RCM. A *Z*-selective catalyst would only be useful in a CM, macrocyclic RCM, or ROCM reaction, so these compounds were not adequate. The low activities of the Schiff base catalysts were attributed to the replacement of a chloride with a phenoxide and to the presence of a tethered dissociating ligand (the imine).[9] Although the phenoxide was an important part of the proposed ligands, it was thought that the catalyst activity would remain high due to the NHC and the monodentate, dissociating phosphine. Additionally, a small loss in reactivity due to the phenoxide may be advantageous; if the catalyst initially forms a *Z*-olefin from two

monosubstituted terminal alkenes and does not react with the 1,2-disubstituted alkene product (no secondary metathesis), there will be no erosion of the *Z*/*E* ratio over time.

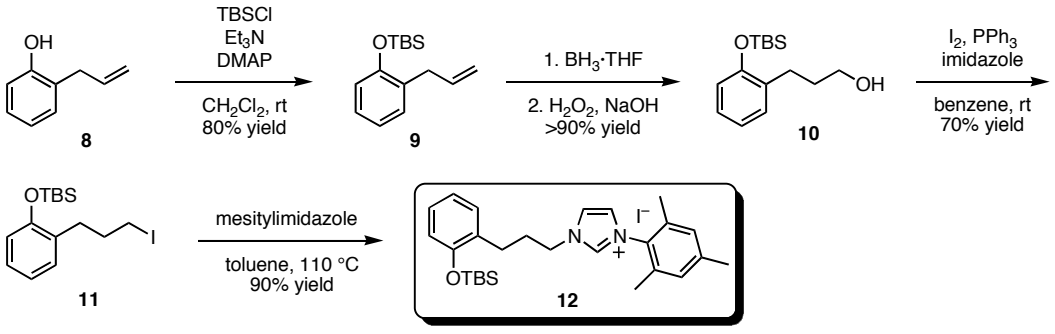


R_1 = substituted aryl ring, Me, CH_2-adamantyl
R_2 = H, 4-NO_2Ph, 6-Me-4-NO_2Ph.

Figure A2.1. Olefin metathesis catalysts bearing Schiff bases.

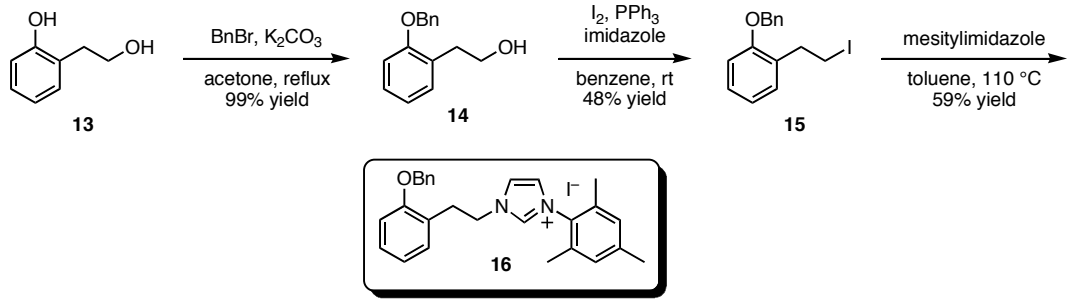
Results and Discussion

A variety imidazolium salts bearing one *N*-bound mesityl ring and one phenol were synthesized. The phenol was tethered to the imidazole ring through one, two, or three methylenes, or it was directly bound to a dihydroimidazole nitrogen atom. The synthesis of the three-methylene tethered phenol NHC precursor **12** is illustrated in Scheme A2.2. The hydroxyl group of 2-allylphenol (**8**) was protected as a TBS ether, and hydroboration/oxidation of the terminal olefin of **9** afforded **10**. The primary alcohol was converted to an alkyl iodide,[10] which reacted with mesitylimidazole to form imidazolium salt **12**.



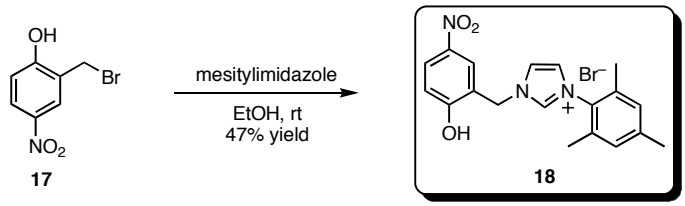
Scheme A2.2. Synthesis of three-methylene linker imidazolium salt.

The ligand with two methylene units separating the phenol from the imidazolium ring (**16**) was generated as shown in Scheme A2.3. The reaction of 2-hydroxyphenethyl alcohol (**13**) with benzyl bromide afforded benzyl ether **14**. As above, the primary alcohol was transformed into a primary alkyl iodide, which was displaced by mesitylimidazole.



Scheme A2.3. Synthesis of two-methylene linker imidazolium salt.

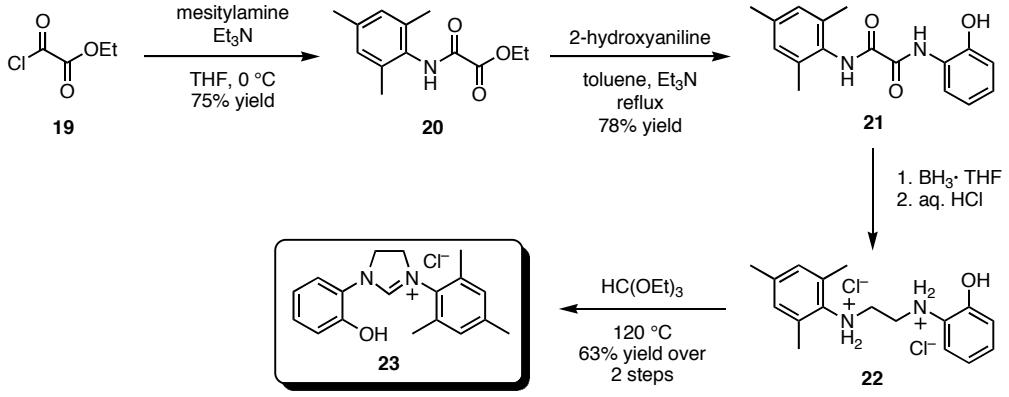
An imidazolium salt that had only one methylene separating the imidazole ring from the phenol (**18**) was made in one step from 2-hydroxy-5-nitrobenzyl bromide (**17**) (Scheme A2.4).



Scheme A2.4. Synthesis of one-methylene linker imidazolium salt.

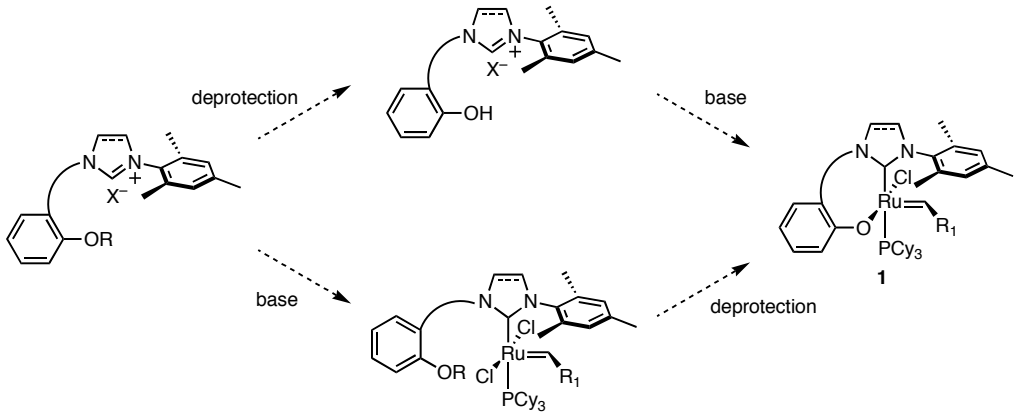
Finally, a compound where the phenol was directly bound to a dihydroimidazolium ring was synthesized (Scheme A2.5). This synthesis was originally developed by Dr. Andrew Waltman, a graduate student in the group at that time.[11] The unsymmetrical diamide **21** was made by first reacting mesitylamine with the acid chloride portion of **19** followed by amidation of the ethyl ester. It was reduced to the

diamine, which was converted to the HCl salt, and **22** was reacted with triethylorthoformate to afford **23**.



Scheme A2.5. Synthesis of unsymmetrical dihydroimidazolium salt.

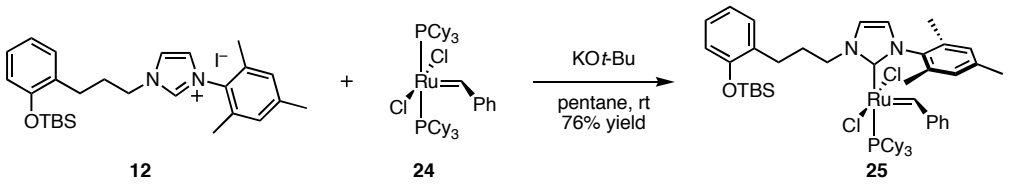
With the desired NHC precursors in hand, metal complexation was explored. Two approaches to accessing the ruthenium compounds were examined: substitution of an L-type ligand with a phenol-protected NHC followed by deprotection, and a one-step procedure where an NHC/phenoxide would replace both an L-type and a chloride ligand in one step (Scheme A2.6). In both case, two steps were needed starting from the phenol protected imidazolium salts.



Scheme A2.6. Two potential synthetic route to the ruthenium complexes.

Ligand substitution followed by phenol deprotection was explored first. When salt **12** was treated with potassium *t*-butoxide in the presence of ruthenium benzylidene

24, the desired mono-phosphine/mono-NHC complex **25** was isolated in 76% yield (Scheme A2.7). This complex displayed characteristic signals in the ^{1}H NMR (CD_2Cl_2) spectrum for mono-NHC Ru benzylidenes. A singlet at 19.2 ppm and a small doublet at 20.1 ppm ($J_{H,P}$ = 12.6 Hz) were present in the ^{1}H NMR spectrum, and a singlet at 34.4 ppm was present in the ^{31}P NMR spectrum. X-ray analysis of suitable crystals of **25** showed that the unsymmetrical NHC ligand was oriented so that the mesityl ring was positioned over the benzylidene phenyl ring (Figure A2.2). It is possible that the doublet at 20.1 ppm in the ^{1}H NMR spectrum arose from a rotamer of **25** where the alkyl chain was positioned over of the benzylidene. Complex **25** catalyzed the ring-closing metathesis reaction of diethyl diallylmalonate to >95% conversion within 30 min at rt.



Scheme A2.7. Synthesis of phenol-protected catalyst **25**.

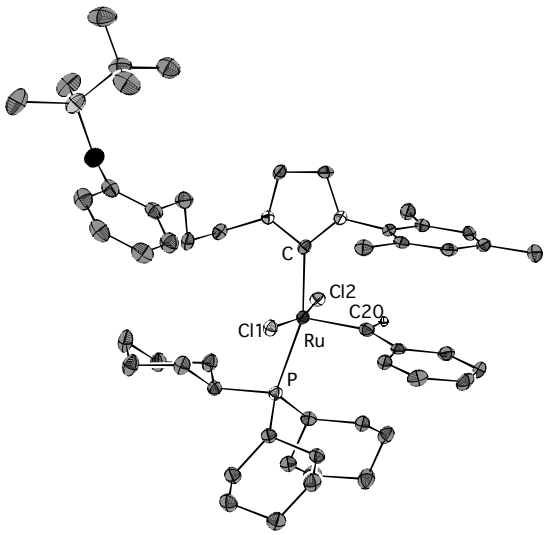


Figure A2.2. Structure of **25** with displacement ellipsoids drawn at 50% probability.

Complex **25** was treated with a variety of fluoride sources, but the TBS group was never removed. Attempts to make the ligand precursor **12** with a more labile TMS group were unsuccessful due to the instability of the trimethylsilyl ether. It was known that a benzyl protecting group could be removed from a hydroxyl located on a ligand bound to a ruthenium benzylidene,[12] so imidazolium salt **16** was reacted with base in the presence of the bisphosphine complex **24**. Unfortunately, pure product was never isolated from this reaction.

In order to avoid the hurdles associated with ruthenium-bound ligand deprotection, the one-step ligand substitution approach was explored. Many combinations of the ligands, ruthenium sources, and bases shown in Figure A2.3 were tested, but no new ruthenium alkylidenes were formed. These reactions were often solvent dependent, but the difference between solvents meant either no reaction occurred or the ruthenium source decomposed. During the course of these experiments, the Hoveyda group reported a chelating NHC-binaphthol ligand bound to a ruthenium alkylidene.[13] Silver carbonate was used as a base/NHC-transfer agent, so this was also attempted with the imidazolium salts in Figure A2.3. Either no reaction or complete decomposition of the ruthenium source occurred.

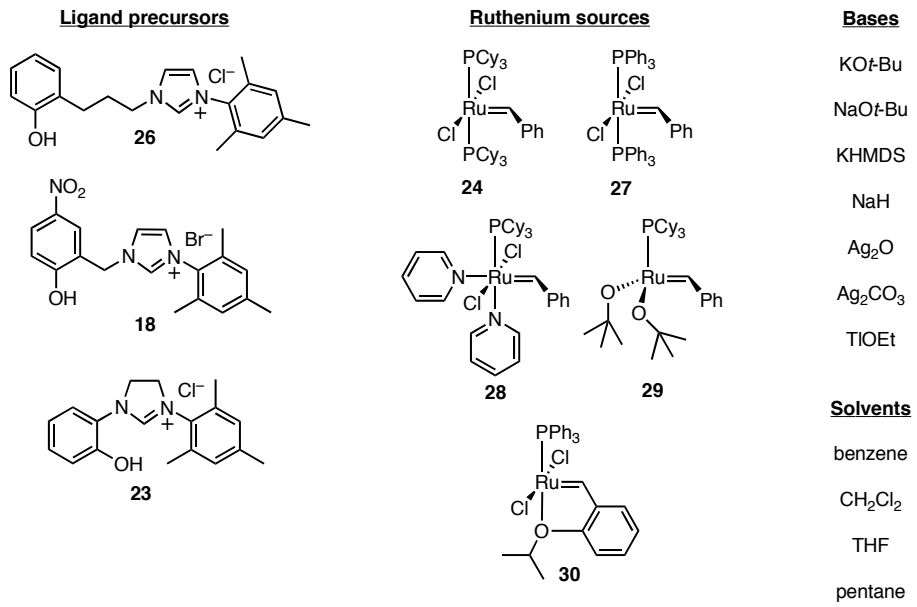
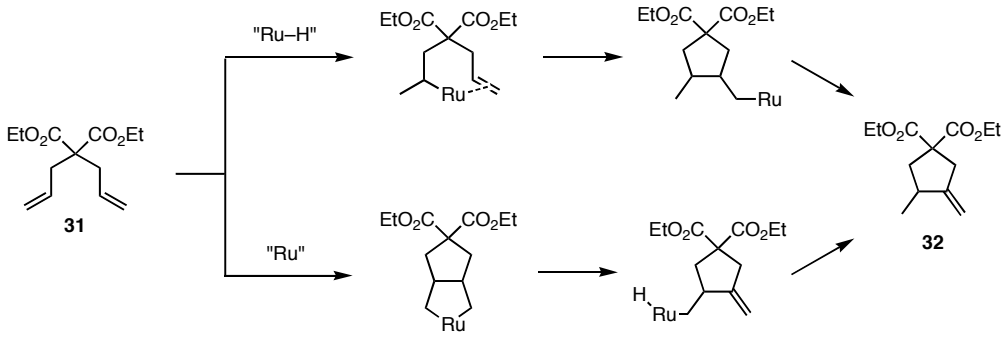


Figure A2.3. Failed attempts to synthesize NHC/phenol bindentate ruthenium complexes.

It was surprising that for many combinations, no reaction was observed. Upon treatment of the unprotected phenol/imidazolium salts with base, presumably both the phenol and the imidazolium were deprotected. Support for double deprotonation was supplied by the fact that, upon treatment with two equivalents of KHMDS, **23** bound to palladium as a bidentate ligand.[11] Because the phenoxide has a negative charge, a metal counterion from the base must be present. Complexation of the counterion by the phenoxide and the carbene could result in species that has low solubility and/or low reactivity to ligand substitution with the ruthenium sources in Figure A2.3. Therefore, compounds that are known to break up metal clusters were added: 18-crown-6, TMEDA, and HMPA.

A combination of **23**, **30**, KHMDS, and one of the additives in benzene-d_6 afforded a mixture of two new alkylidene peaks at 14.9 ppm (doublet, with a peak at 65.6 ppm in the ^{31}P NMR spectrum) and 17.8 ppm (singlet, with no corresponding peak in the ^{31}P NMR spectrum) in the ^{1}H NMR spectrum. Both peaks were present at the same

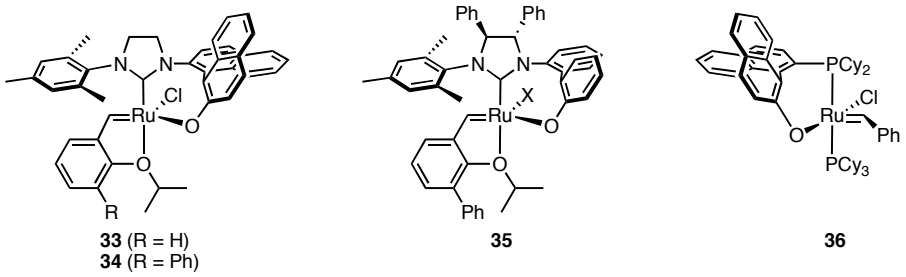
chemical shift regardless of what additive was used, so TMEDA (1 equiv relative to the ligand) was used in scale-up due to its low toxicity and ease of handling. The reactions were not clean, and although the two alkylidenes could be made separately based on reaction temperatures, the impure products never catalyzed the RCM of diethyl diallylmalonate.[14] A new alkylidene with a diagnostic singlet at 16.3 ppm in the ^{1}H NMR spectrum was generated by reacting **26** with **30**, KHMDS, and TMEDA. As with **23**, the reaction was not clean, and the impure ruthenium product did not catalyze the RCM of diethyl diallylmalonate at room temperature. On the other hand, after 21 h at 70 °C, no diethyl diallylmalonate (**31**) was present, but neither was the expected product. A five-membered ring bearing an exocyclic methylene (**32**) was generated either through a ruthenium hydride (Scheme A2.8, upper pathway) or a ruthenacyclopentane (Scheme A2.8, lower pathway). Other ruthenium species, including ruthenium alkylidenes, are known to catalyze this reaction.[15]



Scheme A2.8. Undetermined ruthenium species catalyzing non-metathesis ring closure.

The lack of success of this approach ultimately led to the termination of this project. The NHC/binaphthol complex **33** and other similar bidentate catalysts (**34** and **35**) made by the Hoveyda group were structurally similar to the complexes targeted in this study, and they were not highly metathesis active (Figure A2.4).[13a,16] Interestingly,

they catalyzed the ring-opening cross-metathesis (ROCM) of strained, cyclic alkenes with high *E*-selectivity (>98% *E*-isomer). For reasons that are not clear, catalyst **33**, **34**, and **35** are much more *E*-selective in ROCM than ruthenium catalysts bearing monodentate NHCs. Unfortunately, these complexes were not very active in reactions other than ROCM, such as the CM reaction of allyl benzene and 1,4-diacetoxy-*cis*-2-butene.[17] Additionally, I synthesized a phosphine variant (**36**)[18,19] of the complexes made in the Hoveyda group, but the RCM of diethyl diallylmalonate (**31**) only proceeded to 43% conversion, even at elevated temperatures.



33 (R = H)
34 (R = Ph)

35

36

Figure A2.4. Ruthenium alkylidene complexes bearing biphenyl and binaphthyl ligands.

Conclusion

A series of imidazolium/phenol salts were synthesized to be used as ligands on *Z*-selective ruthenium olefin metathesis catalysts. When the phenol was protected, ligand substitution occurred, and an active metathesis catalyst bearing an unsymmetrical NHC ligand was isolated. Unfortunately, attempts to remove the protecting group were unsuccessful. One-step phosphine/chloride substitution reactions were only achieved when TMEDA, HMPA, or 18-crown-6 were used, and even then the pure products were never isolated. The crude ruthenium alkylidenes did not catalyze RCM, and other structurally similar complexes were not efficient in CM, so no further exploration was

done. The structurally similar catalysts synthesized in the Hoveyda lab are highly *E*-selective in the ROCM of strained rings. An understanding of this selectivity could lend insight into the development of an *E*- or *Z*-selective olefin metathesis catalyst.

Experimental

General Information. All procedures using ruthenium compounds were carried out in a drybox or using Schlenk techniques. Organics were purchased from Aldrich, Alfa Aeser, or Acros and were used as received. Ruthenium compounds **24** and **27** were gifts from Materia. All solvents were purified by passage through activated A-2 alumina solvent columns and were degassed by bubbling through dry nitrogen. All flash chromatography was done using silica gel 60. ^{1}H NMR and ^{31}P NMR (121.388 MHz) spectral data was collected on a Varian Mercury 300 MHz instrument.

(2-Allylphenoxy)-*tert*-Butyldimethylsilane (9).[10] To 2-allylphenol (**8**) (2.0 g, 15 mmol), triethylamine (4.2 mL, 30 mmol), *t*-butyldimethylsilyl chloride (2.7 g, 18 mmol), and *N,N*-dimethylaminopyridine (0.18 g, 1.5 mmol) in a 250 mL round-bottom flask was added CH_2Cl_2 (40 mL). The solution was stirred at rt for 7h, washed with 50 mL brine, 50 mL water, and 50 mL brine. The organic layer was dried over Na_2SO_4 and evaporated to an oil. The product was purified by flash chromatography (100% *n*-pentane) to give 2.96 g (80% yield) of **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05–7.16 (m, 2H), 6.89 (m, 1H), 6.80 (m, 1H), 5.91–6.05 (m, 1H), 5.00-5.08 (m, 2H), 3.38 (d, J = 6.6 Hz, 2H), 1.02 (s, 9H), 0.24 (s, 6H).

3-[2-(*tert*-Butyldimethylsilanyloxy)-Phenyl]-Propan-1-ol (10).[10] To **9** (2.8 g, 11 mmol) in a dry round-bottom flask was added THF (20 mL). The flask was cooled in an ice bath, and a 1M solution of BH_3-THF (11 mL) was added dropwise. After the reaction solution stirred at rt for 3 h, it was cooled in an ice bath. Distilled water (4.8 mL), 10% NaOH (4.8 mL) and 30% H_2O_2 (2.8 mL) were added to the reaction, and it stirred at 0 °C for 3 h. Aqueous HCl (5%) was added until pH 5 was reached, and the reaction mixture was extracted with ethyl ether (2 × 75 mL). The organic layers were combined and washed with saturated $NaHCO_3$ (2 × 30 mL) and brine (2 × 30 mL). It was dried over Na_2SO_4 and evaporated to 3.07 g of **10** as a colorless oil. The crude product was used directly in the next reaction. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.04–7.17 (m, 2H), 6.77–6.93 (m, 2H), 3.62 (t, J = 6.3 Hz, 2H), 2.69 (t, J = 7.6 Hz, 2H), 1.85 (m, 2H), 1.01 (s, 9H), 0.24 (s, 6H).

***tert*-Butyl-[2-(3-Iodopropyl)-Phenoxy]-Dimethylsilane (11).**[10] To crude **10** (1.5 g, 5.4 mmol), imidazole (0.93 g, 14 mmol), and triphenylphosphine (3.1 g, 12 mmol) in a dry round-bottom flask was added benzene (20 mL). The solution was cooled to 0 °C and iodine (2.8 g, 11 mmol) was added. After the solution stirred at rt 1.5 h, pentane (50 mL) was added and a yellow solid precipitated. The reaction mixture was filtered through Celite, and the filtrate was evaporated to a yellow oil. Purification by flash chromatography (100% pentane) afforded 1.43 g (70% yield) of **11** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.05–7.17 (m, 2H), 6.76–6.91 (m, 2H), 3.18 (t, J = 7.1 Hz, 2H), 2.69 (t, J = 7.4 Hz, 2H), 2.11 (apparent quintet, expected t of t, J = 7.4 Hz, 2H), 1.02 (s, 9H), 0.24 (s, 6H).

3-{3-[2-(*tert*-Butyldimethylsilanyloxy)-Phenyl]-Propyl}-1-(2,4,6-Trimethylphenyl)-3*H*-Imidazol-1-ium Iodide (12). To **11** (1.4 g, 3.8 mmol) and mesitylimidazole (0.84 g, 4.5 mmol) in a dry round-bottom flask was added toluene (10 mL). The solution stirred at 110 °C for 24 h. The mixture was cooled in an ice bath, and a tan solid precipitated. It was collected by suction filtration and was washed with ethyl ether to produce 1.91 g (90% yield) of **12** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 10.93 (apparent t, expected dd, J = 1.6 Hz, 1H), 7.46 (apparent t, expected dd, J = 1.6 Hz, 1H), 7.06–7.19 (m, 2H), 7.14 (apparent t, expected dd, J = 1.6 Hz, 1H), 6.99 (s, 2H), 6.76–6.92 (m, 2H), 4.70 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.34 (m, 2H), 2.33 (s, 3H), 2.08 (s, 6H) 1.00 (s, 9H), 0.23 (s, 6H).

3-[3-(2-Hydroxyphenyl)-Propyl]-1-(2,4,6-Trimethylphenyl)-3*H*-Imidazol-1-ium Chloride 26. To **12** (3.0 g, 5.3 mmol) was added ethanol (65 mL) and 2 N HCl (40 mL, 80 mmol). The solution stirred at rt for 14 h, and changed from colorless to orange. Approximately 2 g NaCl was added, and the solution stirred at rt for 24 h. It was neutralized with saturated $NaHCO_3$, and the ethanol was partially removed by evaporation. The solution was extracted with 2 × 150 mL CH_2Cl_2, and the organic layers were combined, dried over Na_2SO_4, and evaporated to an oil. The oil was placed under vacuum, and 1.9 g (99% yield) of **26** as a foamy solid formed. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.71 (apparent broad t, expected dd, 1H), 7.80 (m, 1H), 7.09–7.11 (m, 2H), 6.94–7.00 (m, 2H), 6.97 (s, 2H), 6.73–6.75 (m, 1H), 4.53 (t, J = 6.6 Hz, 2H), 2.62 (t, J = 7.1 Hz, 2H), 2.33 (s, 3H), 2.21–2.26 (m, 2H), 2.04 (s, 6H).

TBS-Phenol/NHC Ruthenium Benzylidene 25. Imidazolium salt **12** (1.03 g, 1.82 mmol), potassium *t*-butoxide (0.2 g, 1.82 mmol), and *n*-pentane (10 mL) were combined in a dry Schlenk flask. After stirring the mixture at rt for 2 h, **24** (1 g, 1.22 mmol) was added as a solid over 20 min. After stirring the resulting mixture for 14 h at room temperature, the pink reaction mixture was cooled to 0 °C and canula filtered. The maroon solid was washed with dry methanol, canula filtered, and dried by vacuum pump to afford 0.9 g (76% yield) of **25** as a maroon solid. Crystals suitable for X-ray diffraction were grown from benzene-pentane vapor diffusion. ^{1}H NMR (300 MHz, CD_2Cl_2, ppm): δ 20.09 (d, J = 13 Hz, 1H)*, 19.20 (s, 1H), 6.70–8.10 (m, 7H), 7.86 (broad s, 2H), 6.30 (broad s, 2H), 4.77 (t, J = 7.5 Hz, 2H), 2.88 (t, J = 8.0 Hz, 2H), 2.40–2.55 (m, 2H), 2.34 (s, 3H), 1.93 (s, 6H), 0.95–1.93 (m, 33H), 1.07 (s, 9H), 0.28 (s, 6H). ^{31}P{^{1}H} NMR (CD_2Cl_2, ppm): δ 34.4 (s). MS (MALDI) 975.24, 977.23. CCDC Reference number 203038.

*This peak is present in the ^{1}H NMR spectrum of the X-ray quality material, and is presumably from the solution-phase rotomer of **25** where the alkyl chain of the NHC/phenol ligand is positioned above of the phenyl of the benzylidene.

2-(2-Benzyloxyphenyl)-Ethanol (14). To a dry round-bottom flask containing 2-hydroxyphenethyl alcohol (**13**) (4.2 g 30 mmol) and acetone (85 mL) was added K_2CO_3 (4.2 g 30 mmol) and benzyl bromide (3.6 mL, 30 mmol). The solution stirred at reflux for 4 h. It was then cooled to rt and stirred 12 h. The reaction mixture was filtered through Celite, and the filtrate was evaporated to a yellow oil. Purification by flash chromatography (20% ethyl acetate in hexanes) afforded 6.87 g (99% yield) of **14** as a

colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.30–7.46 (m, 5H), 7.17–7.24 (m, 2H), 6.90–6.96 (m, 2H), 5.09 (s, 2H), 3.86 (t, J = 6.3 Hz, 2H), 2.97 (t, J = 6.3 Hz, 2H).

2-(2-Benzyloxyphenyl)-Ethyl Iodide (15). To a solution of **14** (6.1 g, 27 mmol) in benzene (90 mL) at 0 °C was added imidazole (2.7 g, 40 mmol), triphenylphosphine (9.1 g, 35 mmol), and iodine (8.8 g, 35 mmol). The reaction solution stirred at rt for 2.5 h. Pentane (125 mL) was added, and a yellow precipitate formed. The mixture was filtered and the filtrate was evaporated to an oil. Purification by flash chromatography (100% pentane) afforde 4.3 g (48% yield) of **15** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.32–7.47 (m, 5H), 7.15–7.29 (m, 2H), 6.91–6.98 (m, 2H), 5.12 (s, 2H), 3.43 (t, J = 8.0 Hz, 2H), 3.28 (t, J = 8.0 Hz, 2H).

[2-(2-Benzyloxyphenyl)-Ethyl]-1-(2,4,6-Trimethylphenyl)-3*H*-Imidazol-1-ium Iodide (16). To **15** (4.3 g, 13 mmol) and mesitylimidazole (2.8 g, 15 mmol) was added toluene (35 mL). The reaction solution stirred at reflux 12 h, and the volatiles were removed. The remaining oil was purified by flash chromatography (2.5% MeOH in $CHCl_3$), and the product was placed under vacuum to provide 3.9 g (59% yield) of **16** as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.47 (br s, 1H), 7.20–7.50 (m, 7H), 6.81–7.12 (m, 4H), 6.97 (s, 2H), 5.14 (s, 2H), 4.95 (t, J = 6.6 Hz, 2H), 3.38 (t, J = 6.6 Hz, 2H), 2.33 (s, 3H), 1.94 (s, 6H).

3-(2-Hydroxybenzyl)-1-(2,4,6-Trimethylphenyl)-3*H*-Imidazol-1-ium Bromide (18). To a solution of 2-hydroxy-5-nitrobenzyl bromide (**17**) (2.0 g, 8.6 mmol) in ethanol

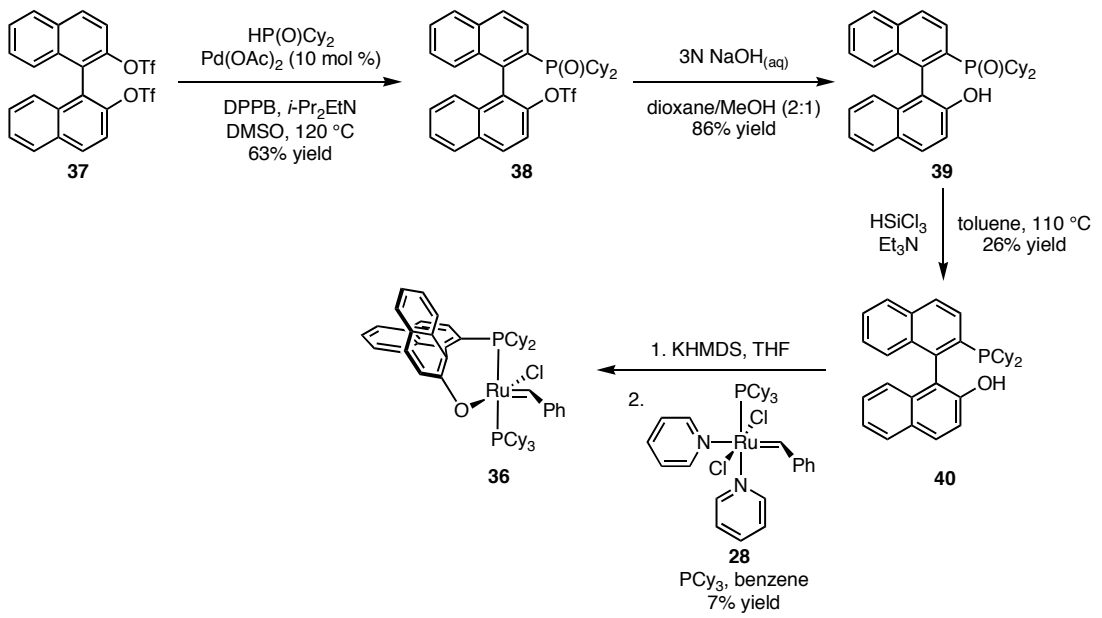
(20 mL) was added mesitylimidazole (1.9 g, 10 mmol). The reaction stirred at rt 1 h. A tan precipitate formed, and it was collected by suction filtration and was washed with ethyl ether to afford 1.7g (47% yield) of **18** as a tan solid. ^{1}H NMR (300 MHz, DMSO-d_6, ppm): δ 9.51 (apparent s, 1H), 8.36 (d, J = 2.7 Hz, 1H), 8.20 (dd, J = 8.8 Hz, 2.7 Hz, 1H), 8.02 (t, J = 1.6 Hz, 1H), 7.90 (t, J = 1.6 Hz, 1H), 7.13 (s, 2H), 7.06 (d, J = 8.8 Hz, 1H), 5.50 (s, 2H), 2.31 (s, 3H), 1.99 (s, 6H).

***N*-(2,4,6-Trimethylphenyl)-Oxalamic Acid Ethyl Ester (20).** To a solution of mesitylamine (5.2 mL, 37 mmol) and triethylamine (10.3 mL, 74 mmol) in THF (100 mL) at 0 °C was slowly added ethyl chlorooxoacetate (**19**) (4.1 mL, 37 mmol). After stirring at 0 °C for 3 h, ethyl acetate (50 mL) and 1 N HCl (100 mL) was added. The organic layer was removed, and the aqueous layer was extracted with 3 × 75 mL ethyl acetate. The combined organic layers were dried over Na_2SO_4 and evaporated to an oil. Upon hexanes addition, a white precipitate formed. The mixture was cooled in an ice bath, and 6.5 g (75% yield) of **20** as a white solid was collected by suction filtration. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.35 (br s, 1H), 6.93 (s, 2H), 4.44 (q, J = 7.1 Hz, 2H), 2.29 (s, 3H), 2.22 (s, 6H), 1.46 (t, J = 7.1 Hz, 3H).

***N*-(2-Hydroxyphenyl)-*N*'-(2,4,6-Trimethylphenyl)-Oxalamide (21).** To **20** (6.5 g, 28 mmol), *o*-hydroxyaniline (3.0 g, 28 mmol), and triethylamine (7.8 mL, 56 mmol) was added toluene (100 mL). The solution stirred at reflux for 17 h. After evaporating the solvent to a small volume, the reaction mixture was cooled in an ice bath. A solid precipitated and was collected by suction filtration. The solid was dissolved in ethyl

acetate (100 mL), and it was washed with 3 × 100 mL 1 N HCl. The organic layer was dried over Na_2SO_4 and was evaporated to afford 6.44 g (78% yield) of **21** as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 9.63 (br s, 1H), 8.79 (br s, 1H), 8.08 (br s, 1H), 7.04 (dd, J = 8.0, 1.6 Hz, 1H), 7.16–7.22 (m, 1H), 7.03 (dd, J = 8.1, 1.6 Hz, 1H), 6.92–6.98 (m, 1H), 6.96 (s, 2H), 2.32 (s, 3H), 2.24 (s, 6H).

3-(2-Hydroxyphenyl)-1-(2,4,6-Trimethylphenyl)-4,5-Dihydro-3*H*-Imidazol-1-ium Chloride (23). To **21** (1.0 g, 3.4 mmol) was added 1 M borane-THF (27 mL, 27 mmol), and the solution stirred at reflux for 12 h. The solution was cooled to rt, and 20 mL MeOH was added, followed by the addition of concentrated HCl until pH 1 was reached. The volatiles were evaporated until only a small volume was present. MeOH (50 mL) was added, and again the solvent was evaporated until only a small volume was present. This was repeated once more with MeOH, and once with EtOH until only a white precipitate was present. The solid (**22**) was collected via suction filtration, and 1.15 g was present. To the white solid **22** (1.15 g, ≤ 3.35 mmol) in a 50 mL round-bottom flask was added triethyl orthoformate (9.0 mL, 54.1 mmol). The mixture was stirred at 120 °C for 13 h, and a yellow precipitate formed. The mixture was cooled in an ice bath, and solid was collected by suction filtration. It was washed with cold hexanes to provide 0.67 g (63% yield) of **23** as a tan solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 8.89 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 6.99–7.05 (m, 2H), 6.99 (s, 2H), 6.76–6.82 (m, 1H), 4.78 (t, J = 10.9 Hz, 2H), 4.36 (t, J = 10.9 Hz, 2H), 2.36 (s, 3H), 2.33 (s, 6H).



Trifluoromethanesulfonic Acid 2'-(Dicyclohexylphosphinoyl)-[1,1']-Binaphthal-enyl-2-yl Ester (38).[19] To racemic 1,1'-bi-2-naphthol bis(trifluoromethanesulfonate) (**37**) (5.0 g, 9.1 mmol), dicyclohexylphosphine oxide (3.9 g, 18.2 mmol), $Pd(OAc)_2$ (200 mg, 0.91 mmol), and 1,4-diphenylphosphinobutane (390 mg, 0.91 mmol) was added DMSO (35 mL) and triethylamine (6.3 mL, 36 mmol). The solution was heated to 120 °C for 15 h. Upon cooling, water (75 mL) was added, and the mixture was extracted with 3 × 150 mL ethyl acetate. The organic layers were combined, dried over $MgSO_4$, and evaporated to a yellow oil which was purified by flash chromatography (45:55 ethyl acetate/hexanes) to afford 3.5 g (63% yield) of **38** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.95–8.08 (m, 4H), 7.46–7.60 (m, 4H), 7.12–7.37 (m, 4H), 0.95–2.09 (m, 22H). $^{31}P\{^1H\}$ NMR ($CDCl_3$): δ 47.3 (s).

2'-(Dicyclohexylphosphinoyl)-[1,1']Binaphthalenyl-2-ol (39). To **38** (3.5 g, 5.8 mmol) was added dioxane (23 mL), methanol (11 mL) and 3 N NaOH (19.2 mL, 58 mmol). The

solution stirred for 14 h at rt, and changed from colorless to yellow. The acidity was lowered to pH 3 by concentrated HCl, and 50 mL water was added. The mixture was extracted with 3 × 100 mL CH_2Cl_2, and the organic layers were combined and evaporated to a white solid. The solid was suspended in a small amount of acetone, ethyl ether was added, and 2.4 g (86% yield) of **39** as a white solid was collected by vacuum filtration. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.69–8.02 (m, 5H), 7.44–7.53 (m, 2H), 7.04–7.28 (m, 4H), 6.52–6.55 (m, 1H), 0.42–2.21 (m, 22H). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 50.7 (s).

2-(Dicyclohexylphosphino)-2'-Hydroxy-1,1'-Binaphthyl (40). To **39** (2.3 g, 5.0 mmol), toluene (80 mL), and triethylamine (23 mL, 170 mmol) in a dry, 200 mL round-bottom flask in an ice bath under N_2 was added trichlorosilane (4.2 mL, 41 mmol). The reaction mixture stirred under N_2 at 110 °C for 13 h. Upon cooling to rt, 80 mL ethyl ether and 10 mL saturated $NaHCO_3$ were carefully added. The mixture was filtered through Celite, washed with ether and toluene, and the filtrate was dried over Na_2SO_4 and evaporated to dryness. The residue was purified by flash chromatography (5% ethyl acetate in hexanes) to afford 0.58 g (26% yield) of **40** as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, ppm): δ 7.81–8.02 (m, 4H), 7.49–7.54 (m, 1H), 7.18–7.34 (m, 6H), 6.89–6.92 (m, 1H), 1.00–2.06 (m, 22H). ^{31}P{^{1}H} NMR ($CDCl_3$): δ –7.4 (s).

Phosphine/Hydroxy Binaphthyl Ruthenium Benzylidene (36). Phosphine/hydroxy binaphthyl ligand **40** (67 mg, 0.14 mmol) and KHMDS (28 mg, 0.14 mmol) were dissolved in THF (2 mL) in a dry Schlenk flask. After stirring 20 min at room temperature, the volatiles were removed by vacuum pump. Complex **28** (100 mg,

0.14 mmol), dissolved in benzene (5 mL), was added to the yellow residual solid. The yellow solid slowly dissolved, and after stirring 30 min at room temperature, PCy_3 (20 mg, 0.07 mmol) in benzene (2 mL) was added to the reaction mixture. The volatiles were removed after 5 min, and the solid residue was purified by flash chromatography (9:1 *n*-pentane/ethyl ether). The fractions containing the light brown band were evaporated to dryness, and the residue was dissolved in a minimum of ether. Pentane was added, the mixture was cooled in an ice bath, and the brown suspension was collected via suction filtration to afford 10 mg (7% yield) of **36** as a brown solid. ^{1}H NMR (300 MHz, C_6D_6, ppm): δ 20.29 (d, J = 4.4 Hz, 1H), 8.37 (d, J = 7.7 Hz, 2H), 6.80–7.96 (m, 15H), 1.00–2.40 (m, 55H). $^{31}P\{^{1}H\}$ NMR (C_6D_6) δ 47.8 (d, J = 230 Hz), 33.2 (d, J = 230 Hz).

X-ray Crystallographic Data

Complex	**25**
Empirical formula	$C_{52}H_{77}Cl_2N_2OPSiRu$
Formula weight	977.19
Crystal habit	Fragment
Crystal size	0.22 × 0.15 × 0.07 mm^3
Crystal color	Yellow
Diffractometer	Bruker SMART 1000
Wavelength	0.71073 Å MoKα
Temperature	98(2) K
Unit cell dimensions	a = 13.6930(7) Å
	b = 13.8481(7) Å
	c =14.7461(8) Å
	α = 106.3870(10)°
	β = 106.6020(10)°
	γ = 92.7590(10)°
Volume	2545.4(2) $Å^3$
Z	2
Crystal system	Triclinic
Space group	P-1
Density (calculated)	1.275 Mg/m^3
Theta range	1.52 to 28.42°
h min, max	–18, 18
k min, max	–18, 18
l min, max	–19, 19
Reflections collected	53070
Independent reflections	11813
R_{int}	0.0704
GOF on F^2	1.136
Final R indicies [I>2σ(I)]	0.0354
Final weighted R [F_o^2]	0.0570

References

[1] (a) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370. (b) Connon, S. J.; Blechert, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 1900–1923.

[2] Lee, C. W.; Grubbs, R. H. *Org. Lett.* **2000**, *2*, 2145–2147.

[3] Morgan, J. P.; Morrill, C.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 67–70.

[4] There are a few examples of substrates that preferentially form cis olefins, such as acrylonitrile and conjugated enynes: see (a) Hoveyda, H. R.; Vézina, M. *Org. Lett.* **2005**, *7*, 2113–2116 and references therein. (b) Kang, B.; Lee, J. M.; Kwak, J.; Lee, Y. S.; Chang, S. *J. Org. Chem.* **2004**, *69*, 7661–7664 and references therein.

[5] Berlin, J. M. California Institute of Technology, 2005, unpublished results.

[6] (a) Tallarico, J. A.; Bonitatebus, Jr., P. J.; Snapper, M. L. *J. Am. Chem. Soc.* **1997**, *119*, 7157–7158. (b) Romero, P. E.; Piers, W. E. *J. Am. Chem. Soc.* **2005**, *127*, 5032-5033.

[7] Chang, S.; Jones, L.; Wang, C.; Henling, L. M.; Grubbs, R. H. *Organometallics* **1998**, *17*, 3460–3465.

[8] De Clercq, B.; Verpoort, F. *Tetrahedron Lett.* **2002**, *43*, 9101–9104. Attempts to reproduce this work in our lab have not been successful. The complexes we have isolated do not have the same spectroscopic properties as those reported.

[9] The rate-determining step in the initiation of Grubbs-type ruthenium catalysts is phosphine dissociation. If one of the L-type ligands does not dissociate, the complex is metathesis inactive. Because the imine is a weaker ligand than PCy_3, it is assumed that it would need to dissociate for the complex to enter a catalytic cycle. But because it is linked to the catalyst through the phenoxide, dissociation is not favorable. For more on catalyst initiation, see (a) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887–3897. (b) Sanford, M. S.; Love, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543–6554.

[10] Ripa, L.; Hallberg, A. *J. Org. Chem.* **1997**, *62*, 595–602.

[11] Waltman, A. W.; Grubbs, R. H. *Organometallics* **2004**, *23*, 3105–3107.

[12] Gallivan, J. P. California Institute of Technology, 2001, unpublished results.

[13] (a) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2002**, *124*, 4954–4955. For another example of silver NHCs, see (b) Arnold, P. L.; Scarisbrick, A. C.; Blake, A. J.; Wilson, C. *Chem. Commun*. **2001**, 2340–2341.

[14] When the reaction was performed at 50 °C in benzene, only the alkylidene at 14.9 ppm was formed. The same reaction run at –10 °C in toluene afforded only the alkylidene at 17.8 ppm.

[15] (a) Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem*. **1999**, *64*, 2178–2179. (b) Fürstner, A.; Liebl, M.; Lehmann, C. W.; Picquet, M.; Kunz, R.; Bruneau, C.; Touchard, D.; Dixneuf, P. H. *Chem. Eur. J*. **2000**, *6*, 1847-1857; (c) Semeril, D.; Olivier-Bourbigou, H.; Bruneau, C.; Dixneuf, P. H. *Chem. Commun*. **2002**, 146-147.

[16] (a) Van Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2003**, *125*, 12502–12508. (b) Van Veldhuizen, J. J.; Campbell, J. E.; Giudici, R. E.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2005**, *127*, 6877–6882. (c) Gillingham, D. G.; Kataoka, O.; Garber, S. B.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2004**, *126*, 12288–12290.

[17] The conversion for this reaction using catalyst **33** was 38% after 53 h at 80 °C, and the *E*/*Z* ratio of the cross product was 3.2:1. At the same conversion using catalyst **24**, the product had an *E*/*Z* ratio of 3.9:1. For more about this standardized reaction and *E*/*Z* selectivities of commonly used ruthenium metathesis catalysts, see Ritter, T.; Hejl, A.; Wenzel, A. W.; Funk, T. W. *Submitted*, **2006**.

[18] See experimental section for details.

[19] (a) Hamada, T.; Chieffi, A.; Ahman, J.; Buchwald, S. L. *J. Am. Chem. Soc*. **2002**, *124*, 1261-1268; (b) Gladiali, S.; Dore, A.; Fabbri, D.; Medici, S.; Pirri, G.; Pulacchini, S.

Eur. J. Org. Chem. **2000**, 2861-2865; (c) Uozumi, Y.; Tanahashi, A.; Lee, S. Y.; Hayashi, T. *J. Org. Chem.* **1993**, *58*, 1945-1948.