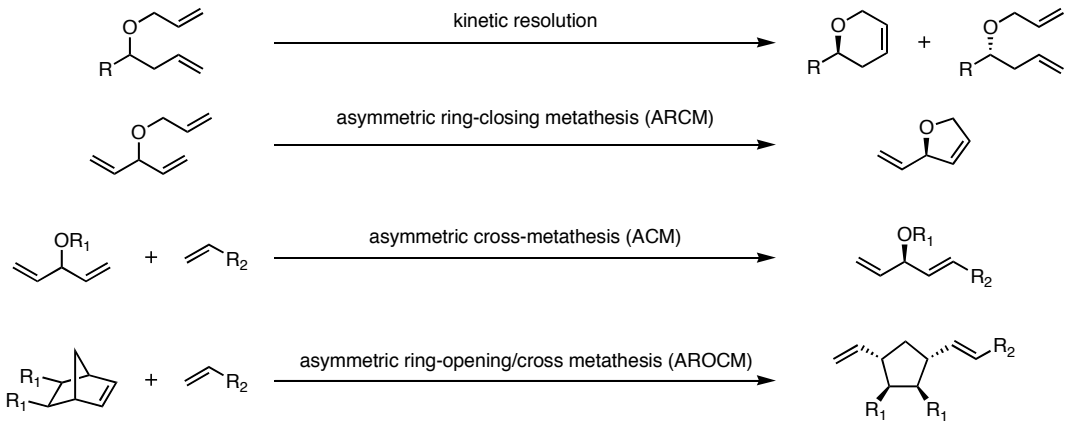
Chapter 4
Asymmetric Ring-Closing Metathesis with Ruthenium Alkylidenes Bearing Chiral, Monodentate *N*-Heterocyclic Carbene Ligands

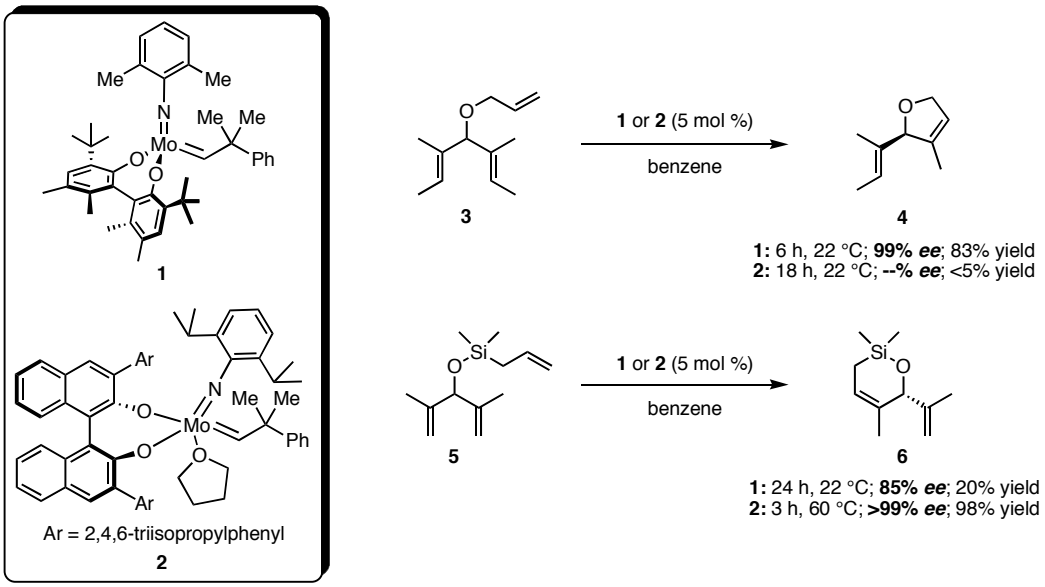
Introduction

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.

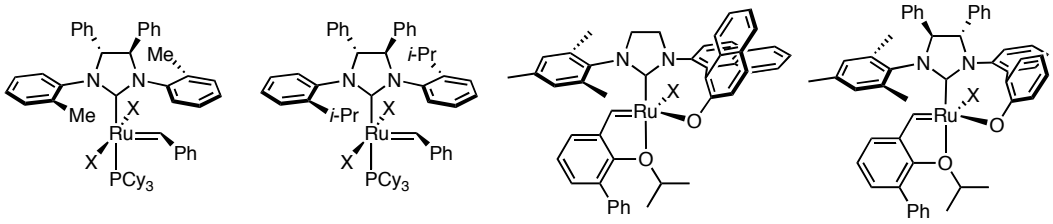
Most asymmetric olefin metathesis reactions have been catalyzed by chiral molybdenum complexes, including kinetic resolutions, ARCM, AROCM, and asymmetric ring-opening/ring-closing metathesis (ARORCM).[1] No single chiral molybdenum alkylidene catalyst is efficient and selective in every asymmetric metathesis 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]

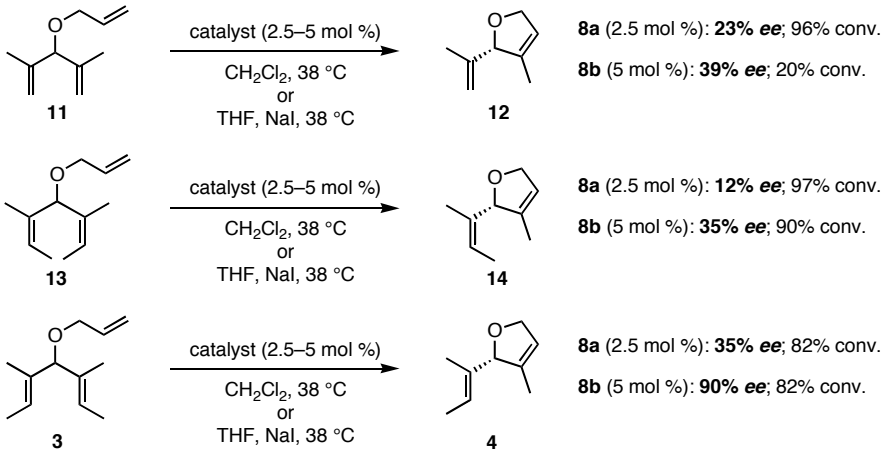


7a (X = Cl) **8a** (X = Cl) **9a** (X = Cl) **10a** (X = Cl)
7b (X = I) **8b** (X = I) **9b** (X = I) **10b** (X = I)

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

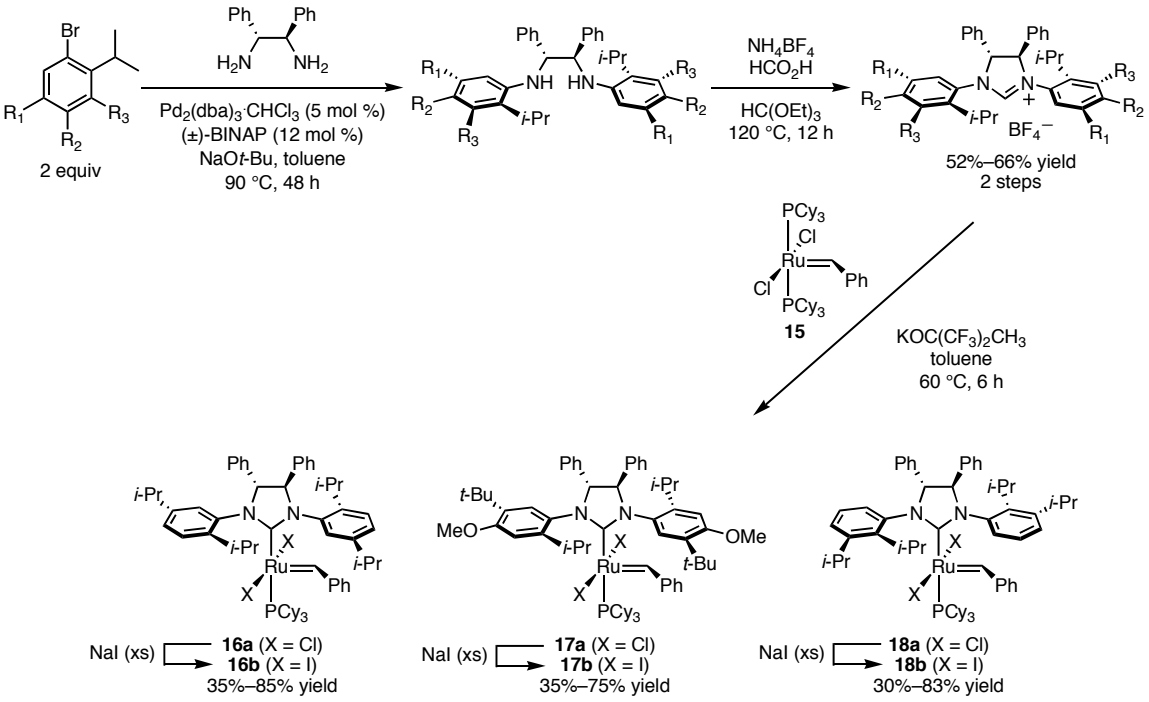
the success of **8** in ARCM, it was expected that these new variants would also be selective and efficient.

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

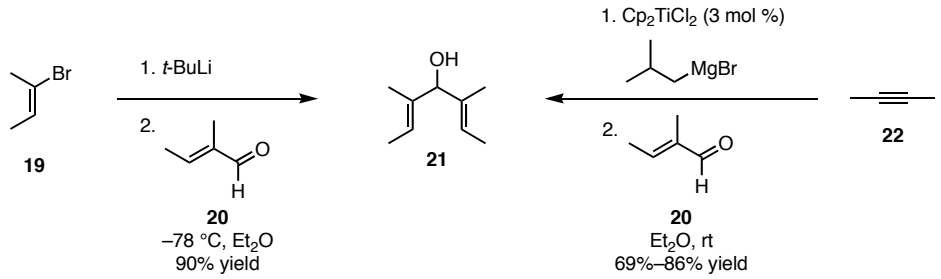
olefin metathesis catalysts as dichlorides. The yields for the last step varied due to a challenging chromatographic purification of the complexes. The para methoxy group in complexes **17a** and **17b** was used as a synthetic handle during the aryl bromide synthesis and was not expected to effect the 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

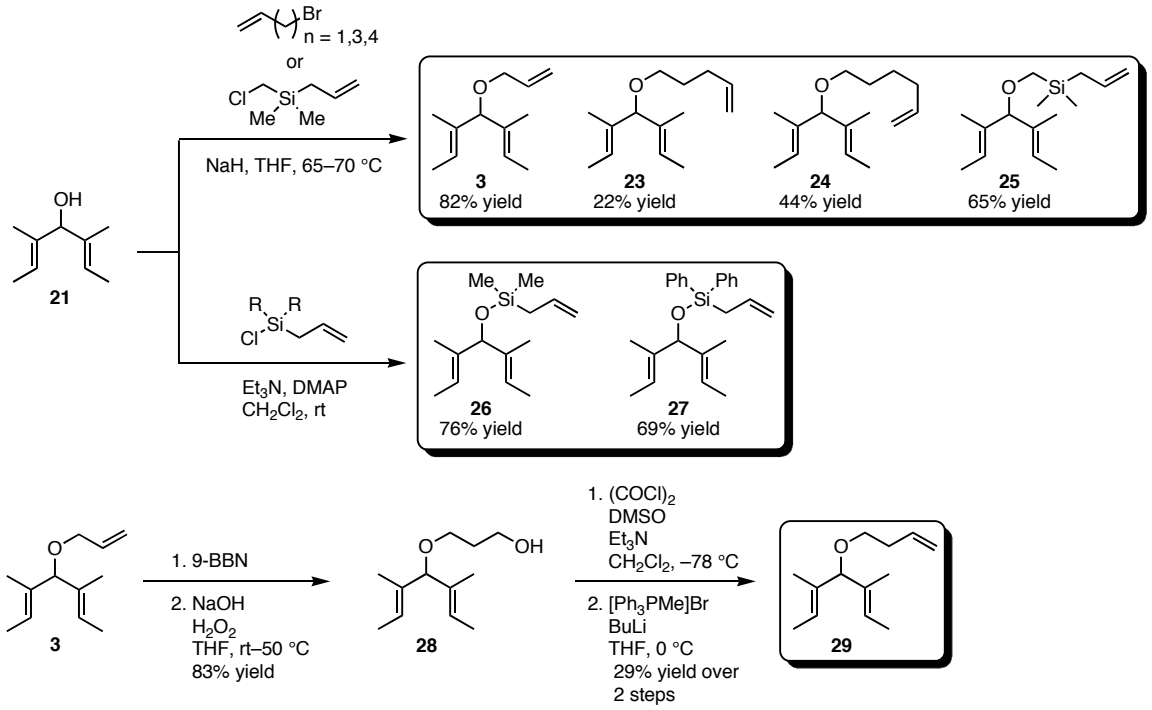
block for all of these substrates was alcohol **21**, and early on in this work **21** was made from vinyl bromide **19** (Scheme 4.5). Compound **19** was commercially available, and **21** was obtained in high yield. As more substrates were made, larger quantities of **21** were needed. Unfortunately, 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.



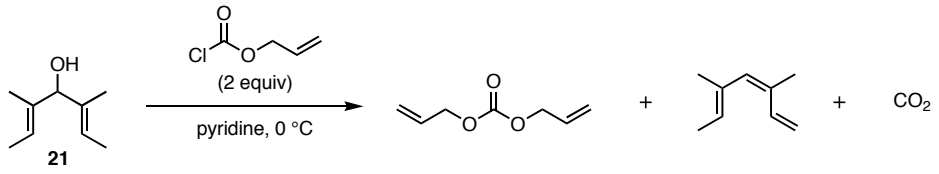
Scheme 4.5. Two approaches to the synthesis of alcohol **21**.

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).



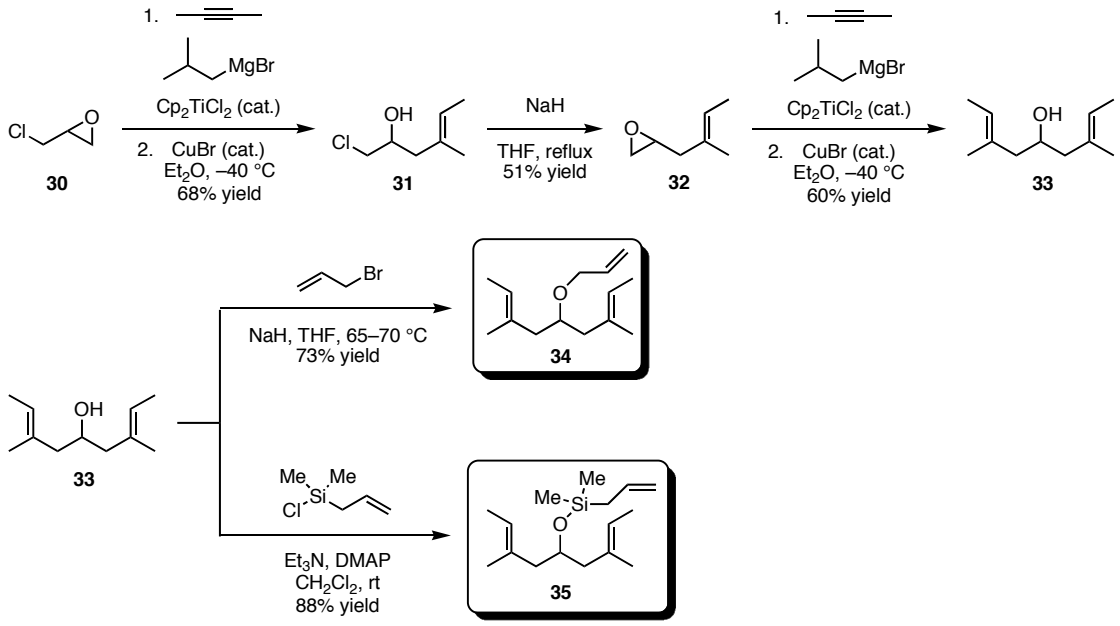
Scheme 4.6. Synthesis of ARCM substrates based on alcohol **21**.



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.

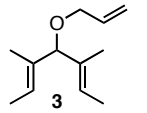
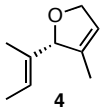
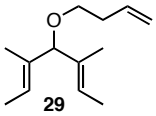
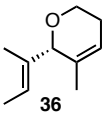
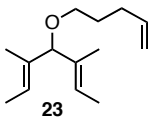
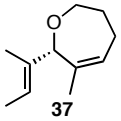
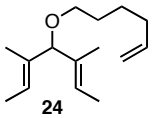
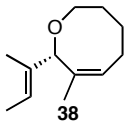


Scheme 4.8. Synthesis of ARCM substrates based on alcohol **33**.

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.

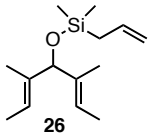
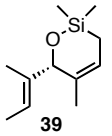
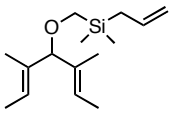
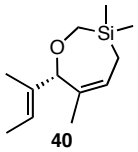
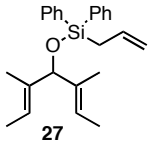
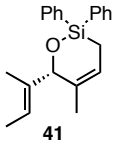
Substrate	Product	8	16	17	18
 **3**	 **4**	**35% *ee***, >98% conv NaI: **90% *ee***, >98% conv	**31% *ee***, >98% conv NaI: **84% *ee***, >98% conv	**30% *ee***, >98% conv NaI: **87% *ee***, >98% conv	**46% *ee***, >98% conv NaI: **90% *ee***, >98% conv
 **29**	 **36**	**68% *ee***, >98% conv NaI: **90% *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

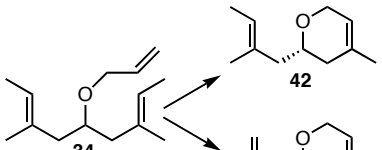
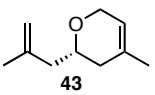
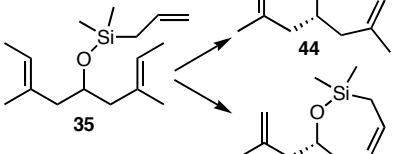
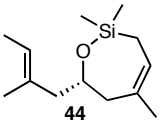
Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. N/D = not determined.

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**.

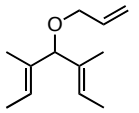
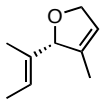
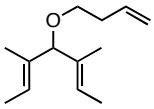
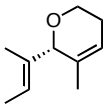
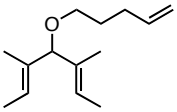
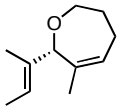
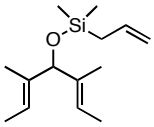
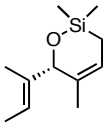
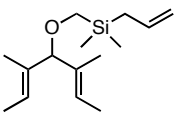
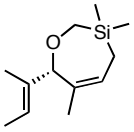
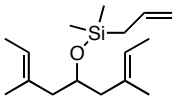
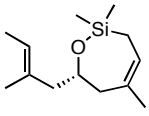
Substrate	Product	8	16	17	18
	**42**	**31%ee**, >95% conv NaI: **35%ee**, >95% conv	**37%ee**, >95% conv NaI: **58%ee**, >95% conv	**23%ee**, >95% conv NaI: **44%ee**, >95% conv	**31%ee**, >95% conv NaI: N/D
34	 **43**	**29%ee**, <5% conv NaI: **38%ee**, <5% conv	**35%ee**, <5% conv NaI: **54%ee**, <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.

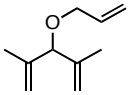
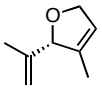
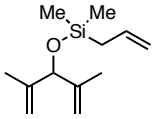
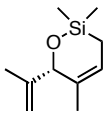
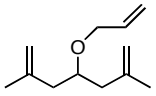
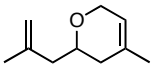
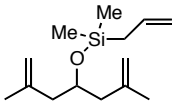
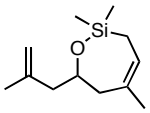
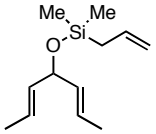
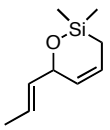
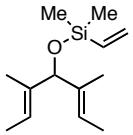
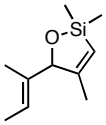
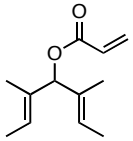
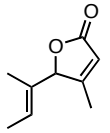
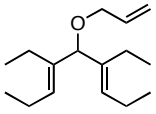
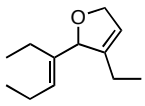
Triene	Product	Catalyst (mol %)	*ee* (%)[a]	Conv. (%)[b]	Yield (%)
 **3**	 **4**	**8b** (4)	90	>98	64
 **29**	 **36**	**8b** (4)	90	>98	77
 **23**	 **37**	**8b** (4)	85	5	N/D
		18a (2)	76	93	92[c]
 **26**	 **39**	**18a** (0.8)	92	>98	77[d]
 **25**	 **40**	**18a** (1)	92	65	64
 **35**	 **44**	**8b** (4)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

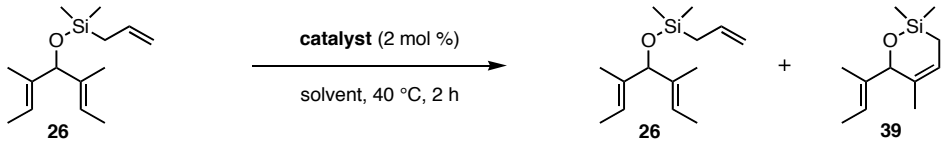
Conditions: dichloride catalyst (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; or dichloride catalyst (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. [a] See appendix 1 for information on an interesting side product. Catalyst **50** = $(H_2IMes)RuCl_2(=CHPh)$. N/A = 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.



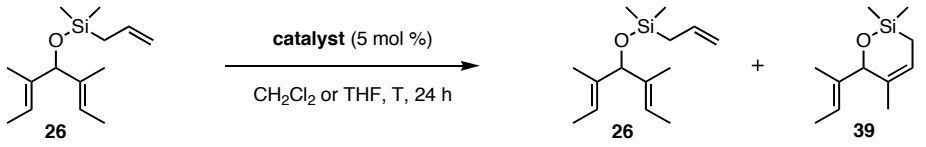
Solvent	Catalyst (mol %)	26 (%)	39 (%)	*ee* (%)
acetone	**50**	>90	<10	N/A
DMF	**50**	>90	<10	N/A
acetonitrile	**50**	>90	<10	N/A
t-butyl methyl ether	**50**	77	23	N/A
ethyl acetate	**50**	67	33	N/A
Et_2O	**50**	9	91	N/A
CH_2Cl_2	**18a**	<2	>98	92
benzene	**18a**	<2	>98	88
THF	**18a**	<2	>98	92

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.

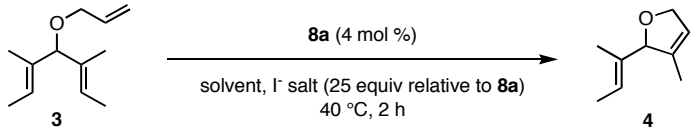


Catalyst (mol %)	Reaction at 0 °C		Reaction at 40 °C	
	ee (%)	Conv. (%)	*ee* (%)	Conv. (%)
8a	88	39	83	>98
8b	90	40	86	68
16b	88	29	90	>98
18a	87	25	92	>98

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.

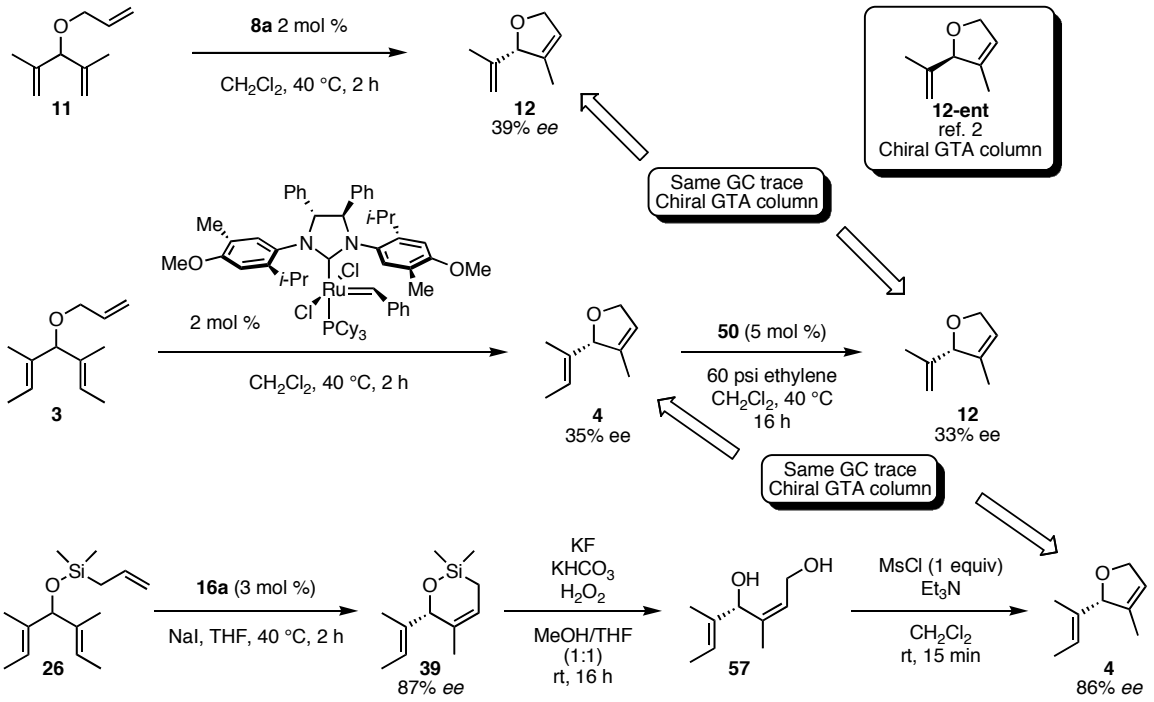
Table 4.8. Effects of iodide source and solvent in ARCM.



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

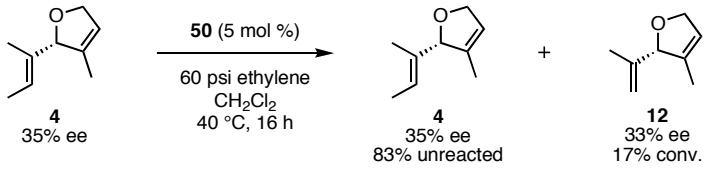
Absolute Stereochemistry Proof. All four chiral ruthenium catalysts tested in this study (**8**, **16**, **17**, and **18**) afforded the same enantiomer of the product for any given substrate in Tables 4.1–4.4, and the absolute stereochemistry of a few of the products was determined (Scheme 4.9). The 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).

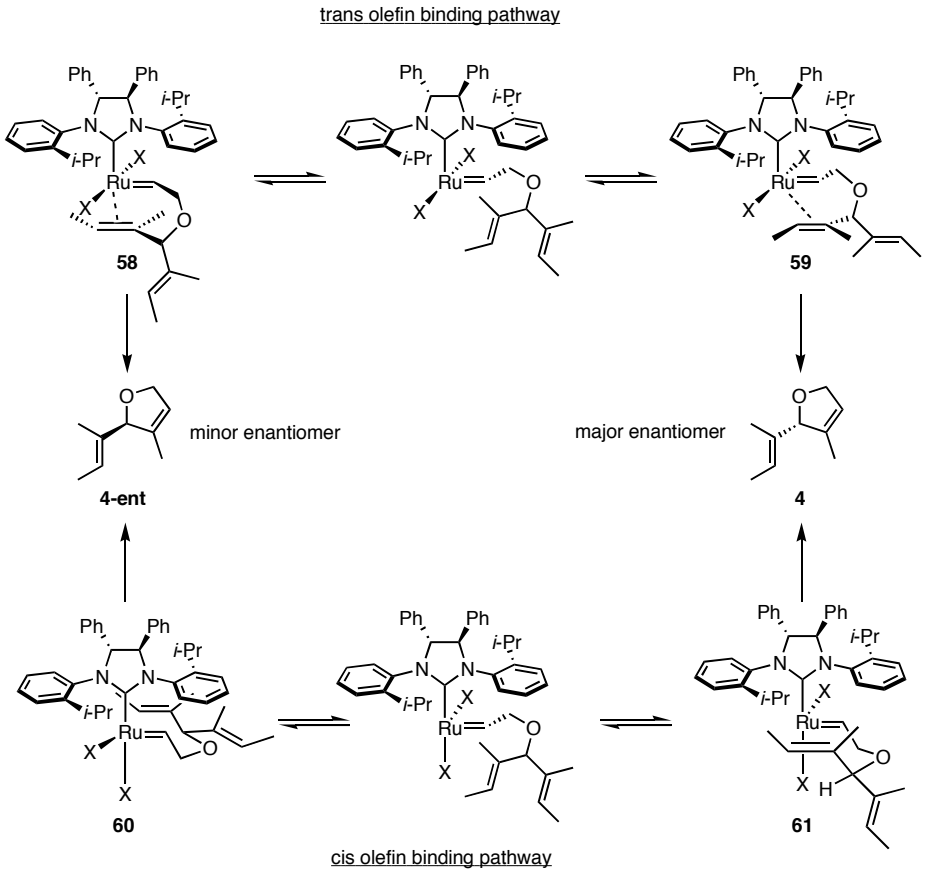


Scheme 4.10. Ethenolysis of **4**.

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**.

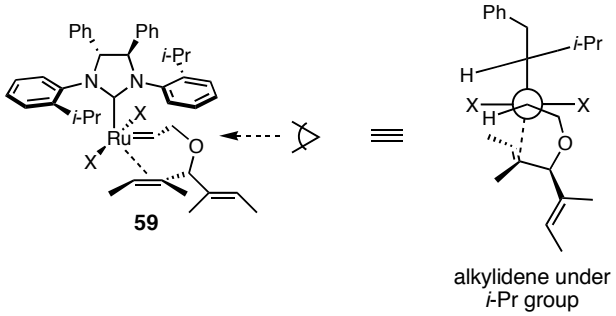


Figure 4.2. Suggested alkylidene position in trans olefin binding pathway.

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,

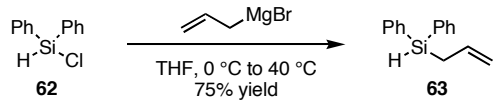
120.9, 114.6, 89.1, 67.5, 30.8, 29.4, 13.4, 12.3. HRMS (EI) *m/z* calc. for $C_{14}H_{24}O$: 208.1827, found 208.1828.

(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.

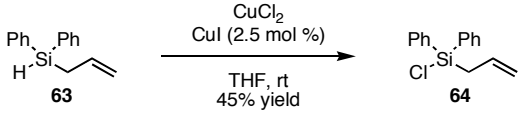
Allyl(((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)methyl)dimethylsilane (25). **21** (300 mg, 2.1 mmol) was added to a suspension of NaH (60% in oil, 103 mg, 2.6 mmol) in 3 mL THF and some bubbling occurred. After 30 min at rt, allylchloromethyldimethylsilane (0.70 mL, 0.63 g, 4.3 mmol) was added, 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.

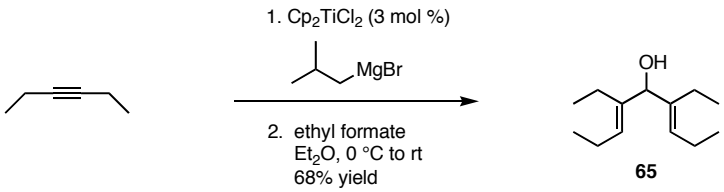
(*E*)-4-Methyl-2-(2-methylbut-2-enyl)-3,6-dihydro-2*H*-pyran (42). Following general procedure B, **34** (23 mg, 0.11 mmol), **8a** (5 mg, 0.005 mmol), and NaI (17 mg, 0.11 mmol) in 2.0 mL THF afforded a crude mixture of **42** (>95%) in 35% *ee* and **43** (<5%) in 38% *ee* (diagnostic peaks at δ 4.78 (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.

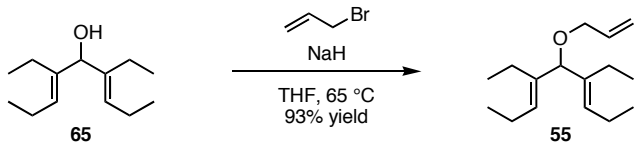
((2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-yloxy)dimethyl(vinyl)silane (51). To a solution of **21** (0.50 g, 3.6 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethylamine (1.5 mL, 11 mmol) and chlorodimethylvinylsilane (0.98 mL, 7.1 mmol). After 12 h at rt, the light brown reaction mixture was poured 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.

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