Chapter 3

Application of Highly Active Chiral Ruthenium Catalysts to Asymmetric Ring-Closing Olefin Metathesis

With the successful synthesis of catalysts **1a,b–5a,b** completed, studies commenced on their application to expanding the scope of ruthenium-catalyzed asymmetric ring-closing metathesis (ARCM) and developing ruthenium-catalyzed asymmetric ring-opening cross metathesis (AROCM) and asymmetric cross metathesis (ACM). This chapter describes my work on ARCM with Dr. Timothy Funk, who was a graduate student at the time. We reported this work together[1] and his complete presentation of the work can be found in his thesis.[2]

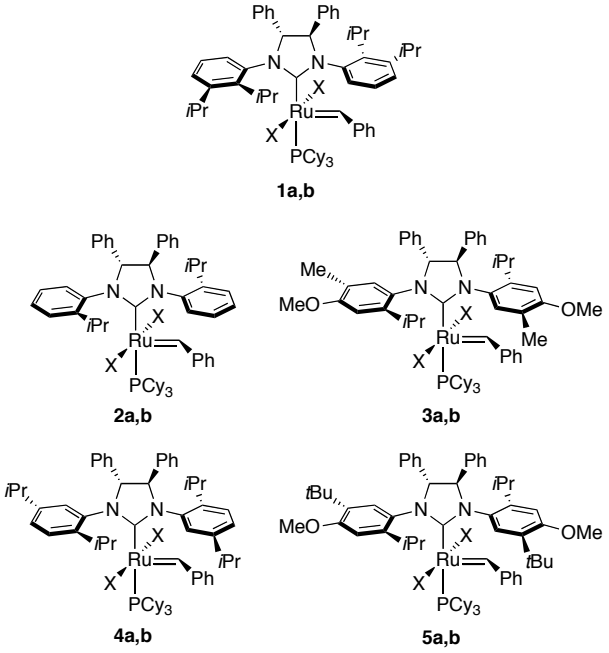


Figure 3.1. Chiral ruthenium olefin metathesis catalysts.

Most ARCM reactions have been catalyzed by chiral molybdenum complexes.[3] For molybdenum-catalyzed ARCM, catalyst to substrate matching is required to obtain high *ee*'s. For example, complex **6** catalyzes the formation of 5-membered ring **9** with high enantioselectivity and yield, but it is inefficient and less selective in generating the six-membered ring **11** (Figure 3.2).[4] On the other hand, catalyst **7** affords **11** in 98%

yield and in >99% *ee*, but is almost completely inactive in the synthesis of **9**.[5] More than 30 chiral molybdenum complexes have been made by varying the imido, alkylidene, and bidentate phenoxide groups.[3b]

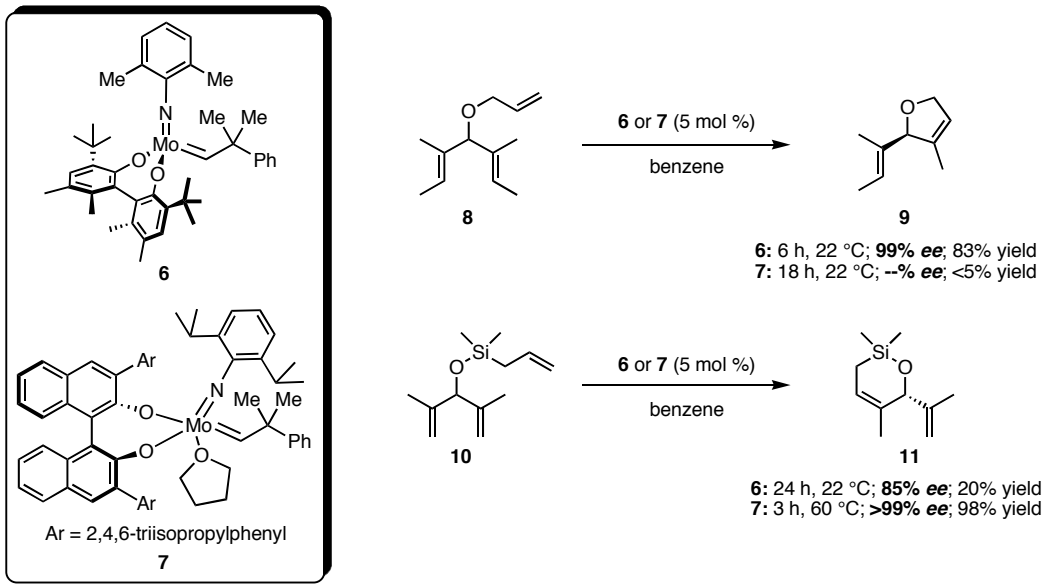


Figure 3.2. Catalyst to substrate matching for chiral molybdenum catalysts.

As mentioned in Chapter 2, like the parent achiral catalysts, the chiral molybdenum complexes are more sensitive to air, moisture, and a variety of common functional groups than most ruthenium olefin metathesis catalysts.[3b] While chiral ruthenium catalyst are more user friendly, only one example of a highly enantioselective RCM reaction was known as we began our work (Figure 3.3).[6]

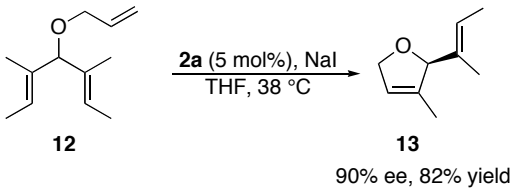
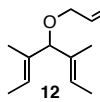
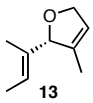
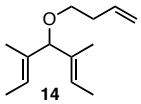
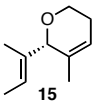
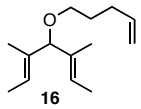
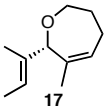
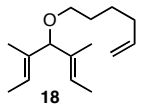
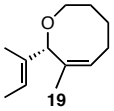
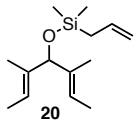
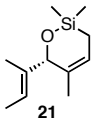
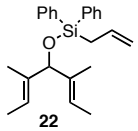
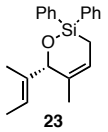
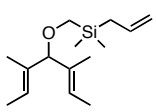
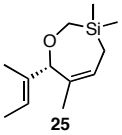
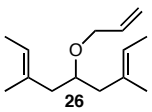
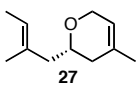
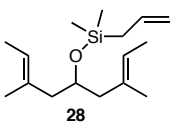
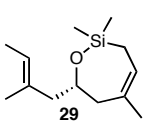


Figure 3.3. Lone example of preexisting successful ruthenium-catalyzed ARCM.

A number of new substrates were examined with catalysts **1a,b–5a,b**. We initially chose to test substrates with the same olefin substitution pattern as **12** because this pattern was

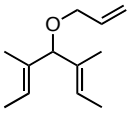
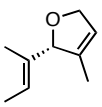
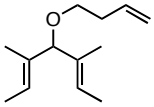
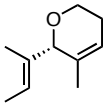
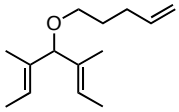
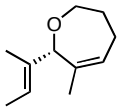
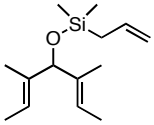
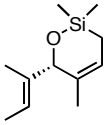
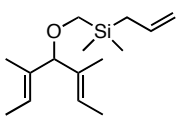
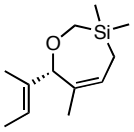
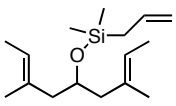
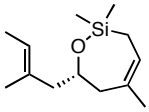
essential to successful ARCM in the initial report. Thus, substrates were prepared with variable linkers attached to the oxygens (**14**, **16**, **18**, **20**, **22**, **24**) and an additional methylene between the prochiral center and each olefin (**26**, **28**). These substrates allowed us to assess the enantioselectivity of the catalysts in forming a variety of ring-sizes and compositions (Table 3.1).

Table 3.1. ARCM with **1–5**

Substrate	Product	1a,b	2a,b	4a,b	5a,b
 **12**	 **13**	**1a** **46% *ee***, >98% conv **1b** **90% *ee***, >98% conv	**2a** **35% *ee***, >98% conv **2b** **90% *ee***, >98% conv	**4a** **31% *ee***, >98% conv **4b** **84% *ee***, >98% conv	**5a** **30% *ee***, >98% conv **5b** **87% *ee***, >98% conv
 **14**	 **15**	**1a** **74% *ee***, >98% conv **1b** **84% *ee***, 70% conv	**2a** **68% *ee***, >98% conv **2b** **90% *ee***, >98% conv	**4a** **67% *ee***, >98% conv **4b** **88% *ee***, >98% conv	**5a** **64% *ee***, >98% conv **5b** **82% *ee***, 43% conv
 **16**	 **17**	**1a** **76% *ee***, 93% conv **1b** **83% *ee***, 20% conv	**2a** **65% *ee***, >98% conv **2b** **85% *ee***, 5% conv	**4a** **56% *ee***, >98% conv **4b** **87% *ee***, 51% conv	**5a** **48% *ee***, 91% conv **5b** **85% *ee***, 70% conv
 **18**	 **19**	**1a** **71% *ee***, ~2% conv **1b** 0% conv	**2a** **65% *ee***, ~1% conv **2b** **85% *ee***, ~2% conv	**4a** **57% *ee***, 4% conv **4b** **88% *ee***, 5% conv	**5a** **51% *ee***, 9% conv **5b** 0% conv
 **20**	 **21**	**1a** **92% *ee***, >98% conv **1b** **92% *ee***, 58% conv	**2a** **83% *ee***, >98% conv **2b** **86% *ee***, 68% conv	**4a** **81% *ee***, >98% conv **4b** **90% *ee***, >98% conv	**5a** **75% *ee***, >98% conv **5b** **85% *ee***, >98% conv
 **22**	 **23**	**1a** **80% *ee***, >98% conv **1b** N/D	**2a** **77% *ee***, >98% conv **2b** **83% *ee***, 96% conv	ND	ND
 **24**	 **25**	**1a** **92% *ee***, 93% conv **1b** **92% *ee***, 10% conv	**2a** **84% *ee***, 88% conv **2b** **87% *ee***, 15% conv	**4a** **80% *ee***, 91% conv **4b** **90% *ee***, 75% conv	**5a** **78% *ee***, 90% conv **5b** **86% *ee***, 50% conv
 **26**	 **27**	**1a** **31% *ee***, >95% conv **1b** ND	**2a** **31% *ee***, >95% conv **2b** **35% *ee***, >95% conv	**4a** **37% *ee***, >95% conv **4b** **58% *ee***, >95% conv	**5a** **23% *ee***, >95% conv **5b** **44% *ee***, >95% conv
 **28**	 **29**	**1a** **52% *ee***, >98% conv **1b** **77% *ee***, >98% conv	**2a** **56% *ee***, 91% conv **2b** **78% *ee***, >95% conv	**4a** **39% *ee***, 80% conv **4b** **74% *ee***, 92% conv	**5a** **36% *ee***, 95% conv **5b** **51% *ee***, 89% conv

Three trends of note emerged from this work: catalyst **2b**, which was used in the initial ARCM report, proved capable of high enantioselectivity for the ring-closing of a variety of other substrates; catalysts **4a,b** and **5a,b** gave results similar to **2a,b** with slight increases in *ee* in some cases and slight decreases in others; on the other hand, catalyst **1a** emerged as the most selective dichloride catalyst. The use of a dichloride catalyst is advantageous because the dichloride catalysts are more active and stable than the diiodide catalysts. Catalysts **1a** and **2b** were selected as the most generally selective catalysts of their classes and were used to obtain isolated yields (Table 3.2). The use of **1a** in ARCM allowed us to decrease the catalyst loading to as low as 0.8 mol %.

Table 3.2. ARCM reactions of selected achiral trienes with chiral ruthenium catalysts

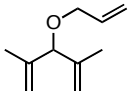
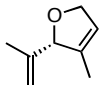
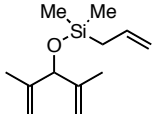
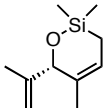
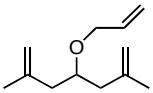
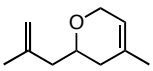
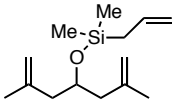
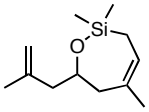
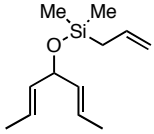
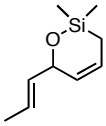
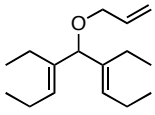
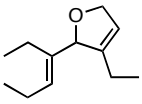
Triene	Product	Catalyst (mol %)	*ee* (%)[a]	Conv. (%)[b]	Yield (%)
 **12**	 **13**	**2b** (4)	90	>98	64
 **14**	 **15**	**2b** (4)	90	>98	77
 **16**	 **17**	**2b** (4)	85	5	ND
		1a (2)	76	93	92[c]
 **20**	 **21**	**1a** (0.8)	92	>98	77[d]
 **24**	 **25**	**1a** (1)	92	65	64
 **28**	 **29**	**2b** (4)	78	>98	98

Conditions for reactions with **2b**: NaI (25 equiv relative to catalyst) and **2a** 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 **1a**: triene, CH_2Cl_2 (0.055 M in triene), and **1a** 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] One mol % of **1a** is added at the beginning of the reaction, and another 1 mol % is added after 2 h. When 2 mol % of **1a** is added at the start with no subsequent additions, the yield was only 74%. [d] Reaction done on a 4 mmol (0.95 g) of **20** scale. ND = not determined.

While we were quite successful in varying the linker attached to the oxygen to prepare a variety of ring systems, efforts to vary the olefin substitution patterns were less successful (Table 3.3). Catalysts **2a,b** consistently gave poor conversion with substrates such as **30, 32, 34,** and **36** that had terminal olefins. This is likely because the methylidene of **2a,b** is highly unstable. Strikingly, when other catalysts such as **5a** or **1a**

were used, excellent conversion was observed. The *ee* remained poor in all cases, but these examples may inform the development of more stable catalysts for olefin metathesis reactions that involve a methylidene species and include a phosphine ligand. Perhaps more disappointingly, poor *ee* was obtained when substrate **40** was used, in which the methyl groups of **11** have been exchanged for ethyl groups. This suggests that with the current catalyst systems, the substrate scope is relatively limited.

Table 3.3. Best results of ARCM reactions with "other" achiral trienes

Triene	Product	Catalyst (mol %)	*ee* (%)	Conv. (%)
 **30**	 **31**	**5a** (2)	39	>98
		4b (4)	64	9
 **32**	 **33**	**5a** (2)	50	93
 **34**	 **35**	**5a** (2)	26	>98
		4b (4)	61	9
 **36**	 **37**	**1a** (2)	–8	>98
		4b (4)	15	18
 **38**	 **39**	$(H_2IMes)RuCl_2(=CHPh)$ (5)	NA	>98 complex mixture
 **40**	 **41**	**2b** (4)	29	>98

Conditions: **1a** or **5a** (2 mol %), triene, CH_2Cl_2 (0.055 M), 40 °C, 2 h; **4a** or **2a** (4 mol %), NaI (25 equiv relative to catalyst), triene, THF (0.055 M), 40 °C, 2 h. NA = not applicable.

We sought to develop a model that explains the enantioselectivity in these reactions, in order to rationally design more reactive and selective catalysts for ARCM.

If the ARCM reaction has a degree of reversibility, a decrease in *ee* over time would be expected. Although this was not observed, further experiments were performed to support the irreversibility of this reaction. When enantioenriched **21** was exposed to achiral catalyst $(H_2IMes)RuCl_2(=CHPh)$ **(42)**, no erosion of the enantiomeric excess was observed, which suggests that once the ring is formed, it does not undergo a secondary ring-opening/ring-closing process. The same conclusion was drawn when enantioenriched **12** was heated under 60 psi of ethylene in the presence of **42** (Figure 3.4). Under these forcing conditions, the enantiomeric excess of unreacted **12** did not erode, and the ethylenolysis product **43** also retained the stereochemistry from the ARCM reaction.

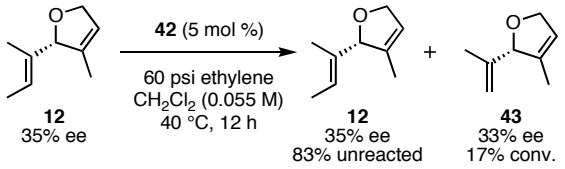


Figure 3.4. Ethylenolysis of **12**.

In the ARCM reactions of the trienes described above, most likely a ruthenium alkylidene derived from the least-substituted olefin initially forms. This species binds one of the diastereotopic olefins, and through a metallacyclobutane intermediate/transition state, forms the ring-closed product. Our initial model[3c] assumed olefin coordination occurred *cis* to the NHC (Scheme 2, lower pathway), on the face opposite the isopropyl group (structure **45**), and that interaction determined the absolute stereochemistry of the product. The interaction of a halide ligand with a substituent on the ring of the cyclic intermediate was also proposed to be an important, stereo-defining

interaction.[7] The actual position of the coordinating olefin relative to the NHC is unclear; experimental evidence exists to support olefin binding both *cis* and *trans* to the NHC (Figure 3.5).[8] In the most recent report on this issue,[9c] Piers and coworkers provide compelling evidence for the observation of a 14-electron ruthenacyclobutane *trans* to the NHC. Computational studies support olefin binding *trans* to the NHC,[9] and a recent computational study of **2b** reacting with **11** calculated that the diastereotopic olefin coordinated *trans* to the NHC (Scheme 2, upper pathway).[10a] Due to the tilt of the *ortho*-substituted *N*-bound aryl ring,[10] the alkylidene is positioned underneath the isopropyl group (structure **47**), which was found to be the "smaller" side of the aryl ring (Figure 3.6), instead of underneath the ortho C—H bond (structure **46**). In addition to the position of the alkylidene determining the absolute stereochemistry of the product, the cyclic intermediate formed upon olefin binding is also important. The pendent olefin not involved in the ring-closing reaction prefers to be in the pseudoequatorial position of the forming ring. Although the discussion presented here focuses on a substrate that forms a 5-membered ring, substrates that form other ring sizes presumably have an energetically favored ring conformation once olefin binding occurs. Therefore the topics mentioned above can be extended to other ring-closing substrates. The importance of the position of the substituents on the ring in the cyclic transition state could explain the higher enantioselectivities observed for the substrates containing dimethylsilyl groups: there are more nonhydrogen substituents on the ring, and therefore the energy differences for various ring conformations are greater than those for substrates with only methylenes in the ring.

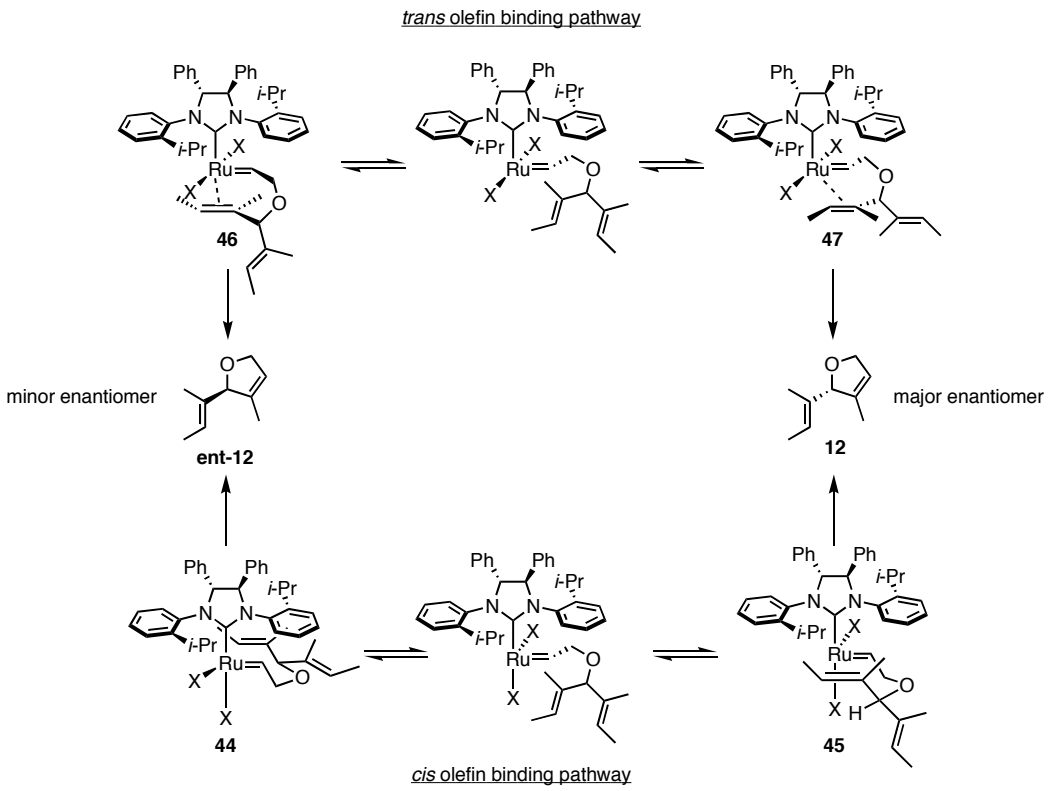


Figure 3.5. Proposed pathways leading to the desired product.

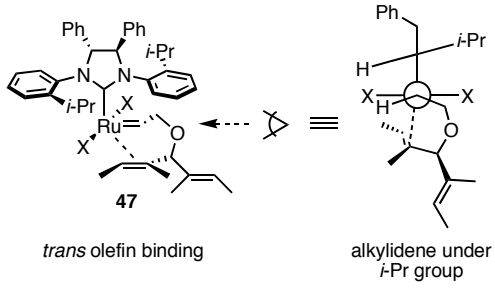


Figure 3.6. Suggested alkylidene position in *trans*-binding transition state.

Our initial *cis*-binding hypothesis was supported by the fact that when a larger halide ligand was present, the enantiomeric excess of the product increased. With recent experimental and computational studies providing evidence for olefin binding *trans* to the

NHC, we sought to relate our experimental data to the suggested *trans*-binding mechanism. If olefin binding occurs *trans* to the NHC, exchanging the chloride ligands for iodides should not have a major steric impact on the transition state.[11] Instead, the iodide ligands may have an electronic effect. When the chlorides in the parent achiral catalyst **42** were exchanged for iodides, phosphine dissociation occurred more rapidly, but the reactivity of the active species did not increase.[12] In the case of the chiral catalysts **1b**-**5b**, a lower reactivity could increase the enantioselectivity by causing the reaction to proceed through a late, more product-like transition state.[13] The added steric bulk in **1a** may hamper its reactivity enough to mimic the electronic deactivation present in the diiodide catalysts **2b**-**5b**, resulting in a late transition state and higher degree of stereochemical communication between the catalyst and the substrate. Substrates **32** and **36**, which have alkenes with less steric hindrance compared to substrates **20** and **28**, may form products in lower enantiomeric excess due to a higher reactivity with the catalyst. Although recent studies suggest olefin binding occurs *trans* to the NHC, and the observed absolute stereochemistry can be justified using a proposed model based on *trans* binding, the experimental data does not provide enough support to rule out a *cis*-binding mechanism.

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 **30**,[5] **31**,[5] **32**,[5] **33**,[5] **34**,[14] **35**,[14] **36**,[14] and **37**[14] are known compounds.

(2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol. Titanocene dichloride (444 mg, 1.78 mmol) was added to a solution of 2-butyne (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 (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 (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol 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) calc for $C_9H_{16}O$, 140.1201. Found 140.1203.

(2*E*,5*E*)-4-(Allyloxy)-3,5-dimethylhepta-2,5-diene (12). (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (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 **12** as a colorless oil. Spectral data matched those in the literature.[4] ^{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) 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 (14). (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (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 **14** 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) calc for $C_{14}H_{24}O$, 208.1827. Found 208.1828.

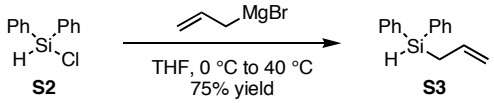
(2*E*,5*E*)-4-(Hex-5-enyloxy)-3,5-dimethylhepta-2,5-diene (18). (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (500 mg, 3.6 mmol) was added slowly to a suspension of NaH (60% in oil, 285 mg, 7.1 mmol) in 7 mL THF at rt, and some bubbling occurred. After 15 min at rt, 6-bromo-1-hexene (0.96 mL, 7.1 mmol) 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 **18** 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) 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 (24). (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (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 **24** 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) calc for $C_{15}H_{28}OSi$, 252.1910. Found 252.1914.

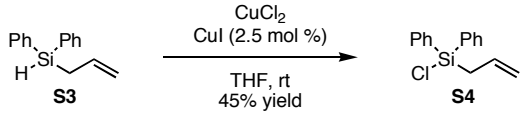
Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)dimethylsilane (20). Allylchlorodimethylsilane (1.1 mL, 7.5 mmol) was added to a solution of (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (1.0 g, 7.1 mmol), triethylamine (1.2 mL, 8.6 mmol), and

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 **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) calc for $C_{14}H_{26}OSi$, 238.1753. Found 238.1752.



Allyldiphenylsilane (S3).[15] To a solution of **S2** (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 **S3** 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 =

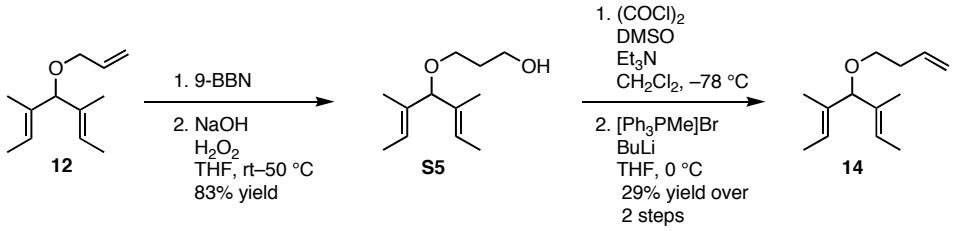
17.1, 1.7 Hz, 1H), 4.88–4.93 (m, 1H), 4.87 (t, J = 3.6 Hz, 1H), 2.15 (dd, J = 7.7, 3.6 Hz, 2H).



Allylchlorodiphenylsilane (S4).[16] 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 (**S3**) (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 **S4** 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).

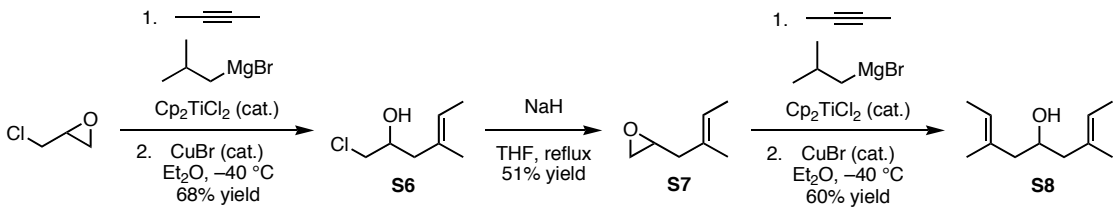
Allyl((2*E*,5*E*)-3,5-dimethylhepta-2,5-dien-4-yloxy)diphenylsilane (22). To a solution of allylchlorodiphenylsilane (**S4**) (370 mg, 1.43 mmol), triethylamine (0.28 mL, 2.0 mmol), and *N*,*N*-dimethylaminopyridine (8.7 mg, 0.07 mmol) in 7 mL CH_2Cl_2 was added (2*E*,5*E*)-3,5-Dimethylhepta-2,5-dien-4-ol (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 **22** 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) calc for $C_{24}H_{30}SiO$, 362.2066. Found 362.2077.



(2*E*,5*E*)-4-(But-3-enyloxy)-3,5-dimethylhepta-2,5-diene (14). **12** (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 **S5** 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 **S5** (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 **14** 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) calc for $C_{13}H_{22}O$, 194.1671. Found 194.1679.



(2*E*,7*E*)-3,7-Dimethylnona-2,7-dien-5-ol (S8). 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 (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 **S6** 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 **S6** (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 **S7** 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 **S7** (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 **S8** 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) calc for $C_{11}H_{20}O$, 168.1514. Found 168.1515.

(2*E*,7*E*)-5-(Allyloxy)-3,7-dimethylnona-2,7-diene (26). Alcohol **S8** (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 **S8** 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 (28). To a solution of **S8** (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 **28** 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) calc for $C_{16}H_{30}OSi$, 266.2066. Found 266.2070.

General Procedure A: asymmetric ring-closing reactions with 1a, 2a, 4a, and 5a. 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 1b, 2b, 4b, and 5b. 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 (13). Following general procedure B, **12** (40 mg, 0.22 mmol), **2a** (8.9 mg, 0.0089 mmol), and NaI (33 mg, 0.22 mmol) in 4 mL THF gave 19.8 mg (64% yield) of **13** 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) 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 (15). Following general procedure B, **14** (40 mg, 0.21 mmol), **2a** (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 **15** 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) 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 (17). Following a modified version of general procedure A, **16** (40 mg, 0.19 mmol) was added to a solution of **1a** (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 **1a** (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 **17** 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) 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 (19). Following general procedure B, **18** (14 mg, 0.061 mmol), **4a** (3 mg, 0.003 mmol), and NaI (9 mg,

0.06 mmol) in 1.1 mL THF afforded **19** as only 5% of a mixture of unreacted **18** 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 (21). Following general procedure A, **20** (0.95 g, 4.0 mmol) and **1a** (35 mg, 0.032 mmol) in 72 mL CH_2Cl_2 gave 0.60 g (77% yield) of **21** 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) 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 (25). Following general procedure A, **24** (40 mg, 0.16 mmol) and **1a** (1.7 mg, 0.0016 mmol) in 2.9 mL CH_2Cl_2 gave 21.7 mg (65% yield) of **25** 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) 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 (29). Following general procedure B, **28** (40 mg, 0.15 mmol), **2a** (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 **29** as a light yellow oil (2% EtOAc in hexanes) in 78% *ee*. 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) calc for $C_{13}H_{24}OSi$, 224.1597. Found 224.1598.

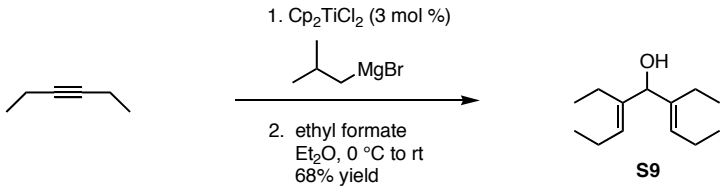
(*S*,*E*)-6-(But-2-en-2-yl)-5-methyl-2,2-diphenyl-3,6-dihydro-2*H*-1,2-oxasiline (23). Following general procedure A, **22** (25 mg, 0.069 mmol) and **1a** (1.5 mg, 0.0014 mmol) in 1.3 mL CH_2Cl_2 gave crude **23** as a pale yellow oil (5% Et_2O in pentane) in 80% *ee*. Chiral SFC (supercritical CO_2 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) calc for $C_{21}H_{24}OSi$, 320.1596. Found 320.1597.

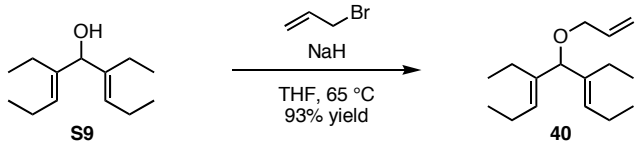
(*E*)-4-Methyl-2-(2-methylbut-2-enyl)-3,6-dihydro-2*H*-pyran (27). Following general procedure B, **26** (23 mg, 0.11 mmol), **2a** (5 mg, 0.005 mmol), and NaI (17 mg, 0.11 mmol) in 2.0 mL THF afforded a crude mixture of **27** (>95%) in 35% *ee*. Chiraldex G-TA, 1mL/min, 60 °C for 70 min, retention times = 60.6 (minor) and 62.4 (major). ^{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 (38). 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[17] (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 **38** 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

(H_2IMes)$RuCl_2$(=CHPh), it was completely converted into a complex mixture of volatile products.



(3*E*,6*E*)-4,6-Diethylnona-3,6-dien-5-ol (S9). 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 **S9** 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).



(3*E*,6*E*)-5-(Allyloxy)-4,6-diethylnona-3,6-diene (40). To a suspension of 95% NaH (24 mg, 1.0 mmol) in 1.5 mL of THF was added **S9** (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 **40** 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) calc for $C_{16}H_{28}O$, 236.2140. Found 236.2140.

(*E*)-3-Ethyl-2-(hex-3-en-3-yl)-2,5-dihydrofuran (41). Following general procedure B, **40** (12 mg, 0.050 mmol), **2a** (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 **41** (>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) calc. for $C_{12}H_{20}O$, 180.1514. Found 180.1510.

Absolute Stereochemistry Proof. All four chiral ruthenium catalysts tested in this study (**1**, **2**, **4**, and **5**) afforded the same enantiomer of the product for any given substrate in Tables 3.1–4.3, and the absolute stereochemistry of a few of the products was determined (Figure S3.1). The absolute stereochemistry of **31-ent** was proven by an independent synthesis using a Sharpless kinetic resolution.[4] Compound **31-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 **2a** catalyzed the formation of **31**, which was also separated on a Chiraldex GTA column. The GC traces showed that chiral catalyst **2a**, and therefore all the catalysts used in this study, afforded **31** in the absolute configuration shown in Table 3.3. The absolute configuration of **13** was determined by exposing it to ethenolysis conditions, which generated the same enantiomer of **31** that was obtained by the ARCM reaction of **30**. Finally, compound **21** was oxidized to diol **S10** and exposed to a one-pot mesylation/intramolecular nucleophilic displacement sequence to afford the same enantiomer of **13** that was obtained by the ARCM of **12**. Chiral, cyclic products derived from a triene lacking terminal methyl groups (**30**), containing cis methyl groups and an alkenyl ether (**12**), and containing cis methyl groups and a dimethylsilyl alkenyl ether (**20**) all had the same absolute stereochemistry, which suggests that all of the products synthesized with **1**, **2**, **3**, **4** or **5** have the same absolute configurations.

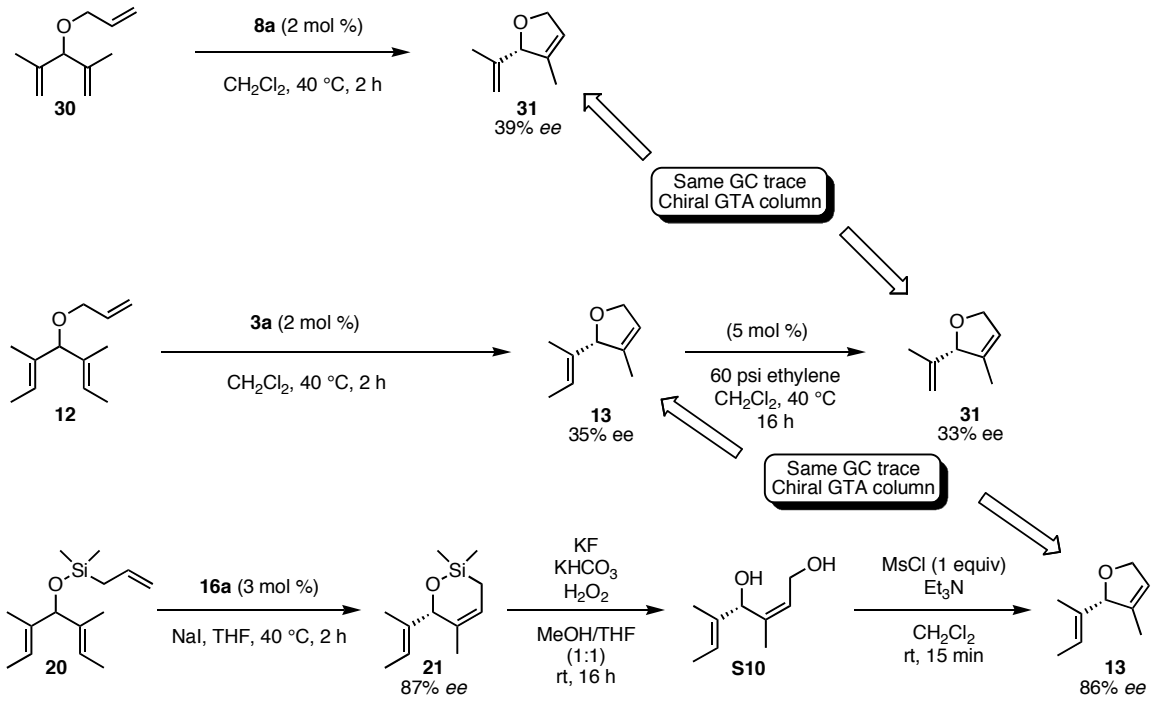


Figure S3.1. Absolute stereochemistry proof.

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[1] Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840.

[2] Funk, T. W. PhD thesis, California Institute of Technology, **2005**

[3] 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. (c) Hoveyda, A. H.; Schrock, R. R. *Chem. Eur. J.* **2001**, *7*, 945.

[4] 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.

[5] 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.

[6] (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 3225. During the course of our work two more reports on Ru-catalyzed ARCM were published: (b) Van

Veldhuizen, J. J.; Gillingham, D. G.; Garber, S. B.; Kataoka, O.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 12502. (c) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2002**, *124*, 4954.

[7] Allowing the hydrogen instead of the non-metal bound vinyl group to interact with the iodide also puts the vinyl group in the pseudo-equatorial position of the ring (see **45**).

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

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

[10] The X-ray crystal structure of an analogue of **2a** in reference 6a shows that the plane of the *N*-bound aryl ring is not orthogonal to the plane of the NHC. QM/MM calculations in reference 9a concluded that the *N*-bound aryl rings of a substrate-bound ruthenium alkylidene also are not orthogonal to the plane of the NHC.

[11] Computations suggest that as the halide ligand increases in size (van der Waals radii) from Cl^- to I^-, the X—Ru—X bond angle also increases. A larger bond angle positions the halides closer to the Ru=CHR moiety (a smaller angle means the halides are pulled

away from the alkylidene), which puts the halides in closer proximity to the reacting olefin, creating a smaller pocket, and therefore a more selective reaction. See reference 9a.

[12] Sanford, M. S.; LOve, J. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 6543.

[13] Palucki, M.; Finney, N. S.; Pospisil, P. J.; Güler, M. L.; Ishida, T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1998**, *120*, 948.

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

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

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

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