Chapter 4

Application of Highly Active Chiral Ruthenium Catalysts to Asymmetric Cross and Ring-Opening Cross Metathesis

In this chapter is described the use of highly active chiral ruthenium catalysts for asymmetric ring-opening cross metathesis (AROCM) and the first example of an asymmetric cross metathesis (ACM) reaction. Chiral molybdenum catalysts have been developed for asymmetric ring-closing metathesis (ARCM) and AROCM.[1,2,3] These catalysts lack extensive functional group tolerance and require rigorous exclusion of air and moisture. The greater functional group tolerance and stability of enantioselective ruthenium metathesis catalysts will dramatically expand the scope and utility of these transformations as has been the case in other areas of olefin metathesis. Described in Chapter 2 was the preparation of a series of highly active chiral ruthenium catalysts (Figure 4.1, Catalysts **2a,b–6a,b**). As described in Chapter 3, catalysts **2a,b–3a,b** and **5a,b–6a,b,** bearing monodentate chiral NHCs, proved to be much more active and selective for ARCM than catalyst **7** that possesses a bidentate chiral NHC and is stereogenic directly at the metal center. In this chapter is described the application of the highly active catalysts to asymmetric ring-opening cross metathesis and asymmetric cross metathesis.

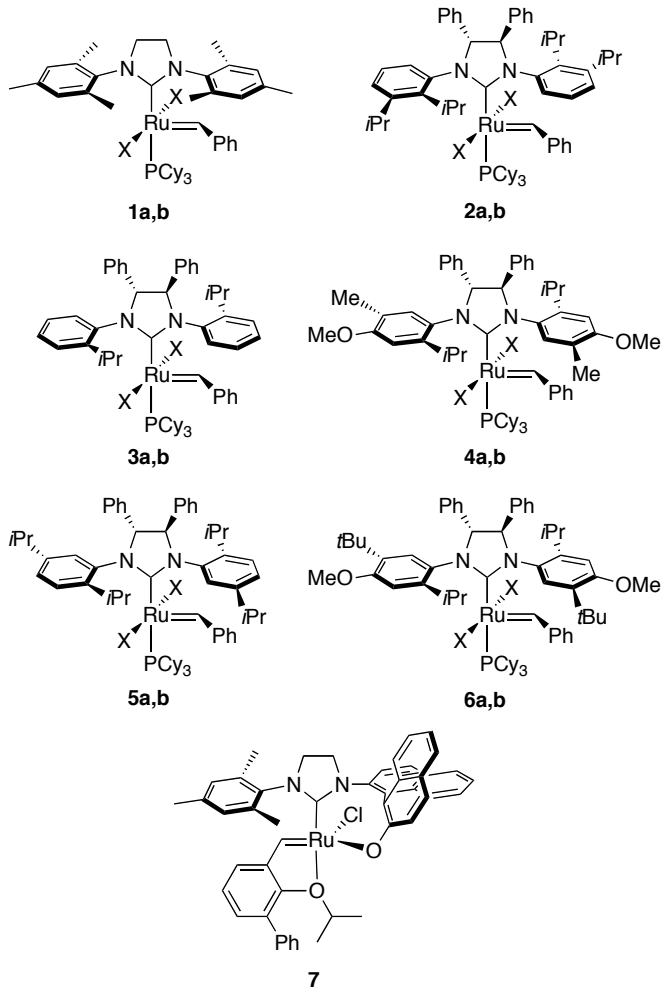
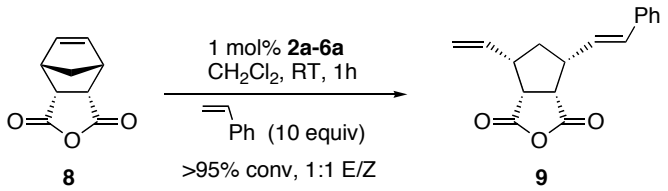


Figure 4.1. Ruthenium olefin metathesis catalysts (**a**: X = Cl, **b**: X = I).

Encouraged by the results for ARCM using **2a**,**b**–**6a**,**b**, the use of these catalysts for asymmetric ring-opening cross metathesis (AROCM) was investigated. Catalyst **7** and related catalysts have been successfully employed in AROCM for a number of norbornenes and related strained bicycles.[4] In an initial study, anhydride **8** was treated with one mole percent of catalysts **2a**, **3a**, **5a**, and **6a** in CH_2Cl_2 in the presence of 10 equivalents of styrene (Table 4.1).

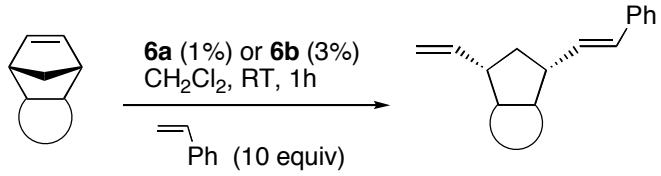
Table 4.1. AROCM with chiral ruthenium catalysts

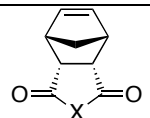
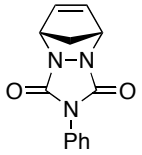
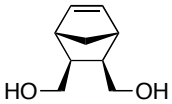
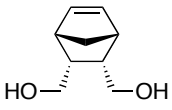
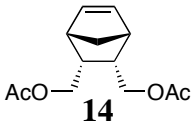


Catalyst	Product	*ee*
2a	*ent*-**9**	47%
3a	*ent*-**9**	29%
5a	**9**	62%
6a	**9**	76%

Catalyst **6a** was the most selective of the dichloride catalysts, and no change in enantioselectivity was observed when the solvent (CH_2Cl_2, $CHCl_3$, THF, Et_2O, benzene, toluene, neat) or equivalents of cross partner (1, 3, 5 and 10) were varied. In ARCM reactions, the diiodide catalysts **2b**–**6b** were found to be dramatically more enantioselective than the dichloride catalysts **2a**–**6a**. In the current system, the use of **6b** instead of **6a** improved the *ee* slightly to 80% and cooling the reaction to 0 °C gave **9** in 82% *ee*. The diiodide catalysts are generally less reactive than the dichloride catalysts; therefore, the loading of **6b** was increased to three mole percent in order to achieve activity similar to **6a**. Since catalysts **6a,b** gave the highest *ee* for substrate **8**, they were employed to explore the substrate scope (Table 4.2).

Table 4.2. AROCM using **6a** and **6b**



Substrate	Catalyst[a,b]	*ee* E(Z)	Yield (E/Z)
 **8** X=O	**6a**	76% (4%)	95% (1:1)
	6b	80% (n.d.)	96% (1:1)
10 X=N-*t*Bu	**6a**	57% (33%)	99% (1.4:1)
	6b	75% (50%)	99% (1.2:1)
 **11**	**6a**	68% (15%)	99% (1.2:1)
	6b	68% (10%)	99% (1.2:1)
 **12**	**6a**	33% (29%)	30% (1.1:1)
 **13**	**6a**	81% (20%)	10% (ND)
 **14**	**6a**	60% (10%)	99% (1.4:1)
	6b	72% (40%)	78% (1.4:1)

[a]Conditions for **6a**: 1 mol%, CH_2Cl_2, RT, 10 equiv styrene, 1h.
[b]Conditions for **6b**: 3 mol% **6a**, 1 equiv NaI, CH_2Cl_2, RT, 10 equiv styrene, 1h.

The E/Z ratio was close to one to one for all of the substrates examined, but we initially focused our attention on discovering trends within the trans series of products because in

all cases the *ee*'s of the cis products were lower than the *ee*'s of the trans products. Replacement of the anhydride oxygen with a *tert*-butylamine (**10**) reduced the enantioselectivity to 57% for **6a** and 75% for **6b** and both catalysts gave quantitative yields. Introducing heteroatoms into the norbornene skeleton (**11**) slightly reduced the *ee* to 68% and surprisingly catalysts **6a** and **6b** afforded product in the same *ee*. When unprotected diols **12** and **13** were examined the yields were dramatically reduced to 30% and 10% respectively. In these cases, substrate coordination to the catalyst may inhibit the reaction. In addition, the stereochemistry of the norbornene diols affected the *ee* as the *endo*-diol **13** gave 81% while the *exo*-diol **12** gave only 33%. To prevent coordination to the catalyst, diol **13** was protected as a bisacetate (**14**) which resulted in a decrease in *ee* to 60% accompanied by a large increase in yield to 99%; the use of catalyst **6b** improved the *ee* to 72% and slightly reduced the yield to 78%. The cis series of products exhibited different selectivity trends than the trans series. The cis *ee* both increased when the trans *ee* decreased (**8** vs. **10** with **6a**) and decreased when the trans *ee* increased (**10** vs. **11** with **6a**). In addition, when catalysts **2a,b**–**5a,b** were examined with these substrates, catalysts **6a,b** always gave the trans product in the highest *ee*. However, catalysts **5a,b** often gave the cis product in the highest *ee*.

Careful evaluation of the data obtained thus far elucidates some aspects of the mechanism for AROCM and allows for a proposal as to the origin of enantioselectivity. Upon monitoring the reactions of **8** and **10** over 3 hours, no change in the E/Z ratio or *ee* was observed. Moreover, the reactive terminal olefin in the products is never observed to undergo further cross metathesis reactions at RT. These findings indicate that the products are unreactive towards secondary metathesis and therefore that the *ee*'s and E/Z

ratios observed are the direct result of singular reactions with the catalysts. Of primary importance to the development of a mechanism for AROCM is to distinguish between the two possible ruthenium alkylidene propagating species (Figure 4.2).

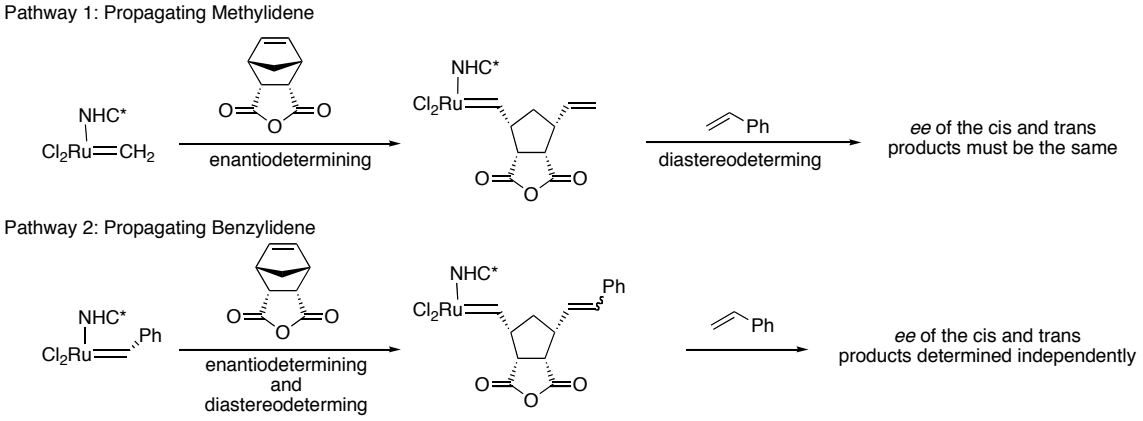


Figure 4.2. Comparison of propagating species.

In pathway 1, the norbornene reacts with a ruthenium methylidene intermediate and this ring-opening step determines the *ee* of the products. Then in the cross metathesis step the products are released, determining the olefin geometry of the products and regenerating the ruthenium methylidene. This pathway requires that the *ee* of both the E and Z products be identical. In pathway 2, the norbornene reacts with a ruthenium benzylidene intermediate and both the *ee* and olefin geometry of the products are determined concurrently in this ring-opening step. The products are then released in the cross metathesis step that regenerates the ruthenium benzylidene. The *ee*'s of the E and Z products are independent in this reaction pathway. Since the observed *ee*'s of the E and Z products are significantly different, we propose that it is likely that the ruthenium benzylidene is the propagating species in this system.

There has been a long standing debate regarding the site of olefin coordination to the ruthenium catalyst that leads to metallocyclobutane formation. There is experimental

evidence that supports olefin binding either cis or trans to the NHC.[5] In the most recent report on this issue,[5c] Romero and Piers provide compelling evidence for the observation of a 14-electron ruthenium species in which the metallocycle lies trans to the NHC. Computational studies also support olefin binding trans to the NHC,[6] in fact, a recent computational study of **3b** in ARCM calculated olefin coordination trans to the NHC as the lower energy pathway.[6a]

In our system, catalyst **3a** yields *ent*-**9** and catalyst **6a** yields **9** as the major trans product.[7] Moreover, the propagating species is believed to be a benzylidene and norbornenes are well known to react preferentially on the exo face of the olefin.[8] With these caveats in mind, a cis coordination pathway would require that the norbornene approach catalyst **3a** from the face that is shielded by the *ortho*-isopropyl group and catalyst **6a** from the face that possesses the *meta-tert*-butyl group (Figure 4.3).

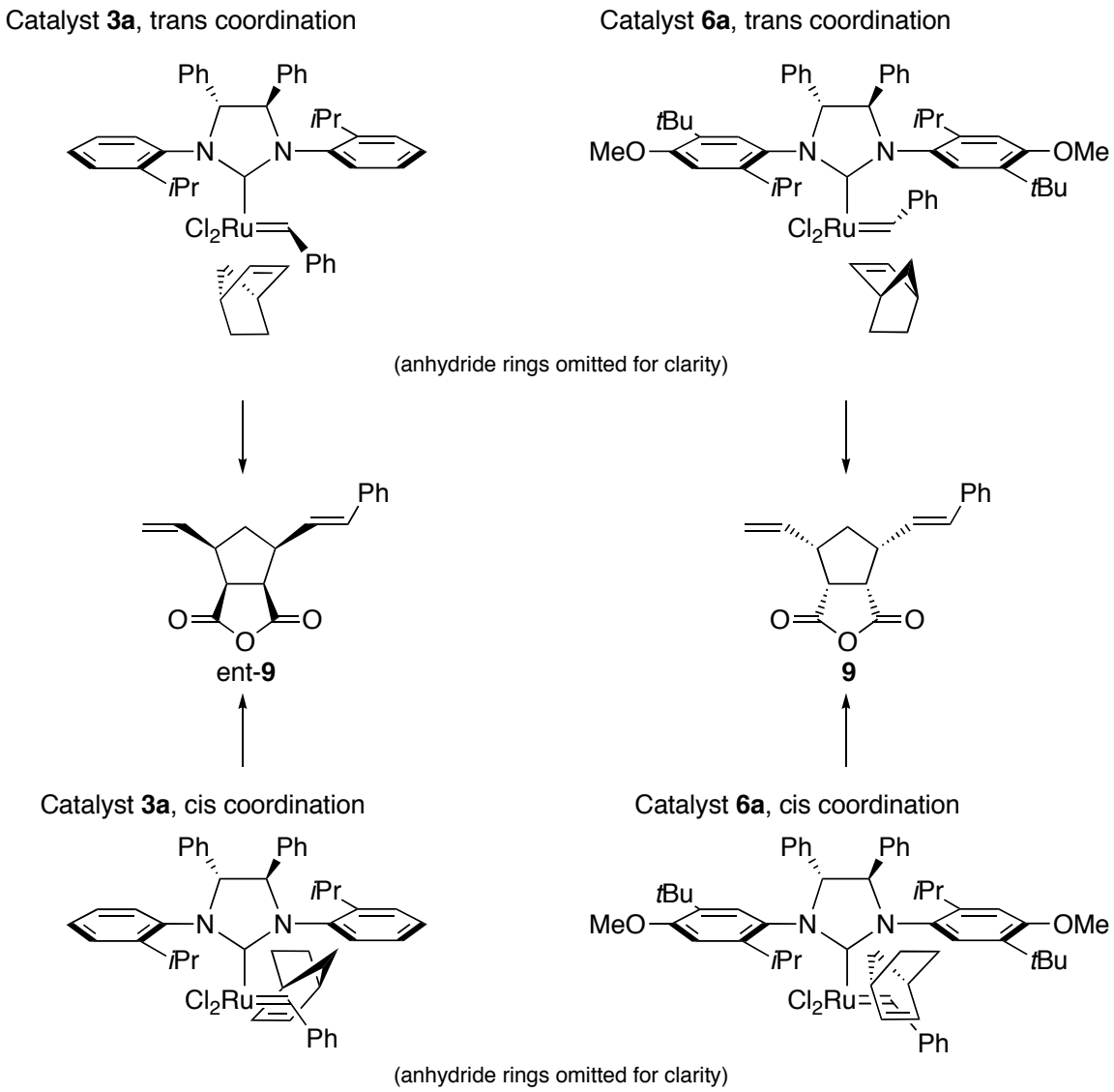


Figure 4.3. Olefin approaches for **3a** and **6a** that afford the major trans enantiomer.

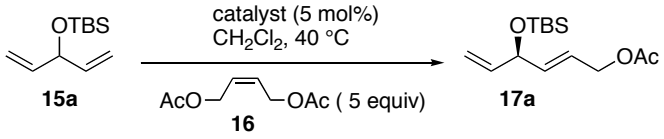
It is most likely that introducing a *tert*-butyl group in the meta position increases the steric bulk of that side of the ring. Therefore, at this time, the cis coordination pathway seems unlikely as it requires the norbornene to approach both catalyst **3a** and **6a** from the more hindered side.

It is proposed that a trans coordination pathway is more consistent with the observed data. A trans coordination pathway would require that the benzylidene of catalyst **3a** sit under the unsubstituted side of the aryl ring, and the benzylidene of

catalyst **6a** sit under the side bearing an *ortho*-isopropyl group. Thus increasing the steric bulk of the *tert*-butyl side of the ring causes the benzylidene to move to the opposite side of the ring, explaining the observed reversal of enantioselectivity between these two catalysts. Continued work on asymmetric metathesis will allow for further development of this mechanistic insight.

Catalyst **1a** has been used extensively in cross metathesis[9] and a chiral variant of this transformation would provide a powerful new synthetic tool for the construction of stereochemically complex targets. However, ACM is also the most challenging of the asymmetric metathesis transformations, as only in this transformation must all three factors – the propagating species, its orientation, and enantiotopic olefin selection - be controlled. ACM work was carried out in collaboration with Dr. Steven Goldberg. In ARCM, there is only one possible propagating species that leads to productive metathesis, so only the orientation of that species and the selection of an enantiotopic olefin must be controlled. AROCM requires control of the propagating species and its orientation, but facial selectivity of the enantiotopic olefin is easily controlled in the norbornene substrate. To address the enantiotopic olefin selection in ACM, we focused on meso diene substrates that had distinct small (H), medium (vinyl) and large (OP) substituents at the allylic carbon. To address the nature of the propagating species, we employed TBS protected 1,4-pentadiene-3-ol (**15a**) and cis-1,4-diacetoxy-2-butene (**16**) as substrates (Table 4.3).

Table 4.3. ACM using catalysts **2a**–**6a**

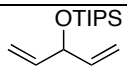
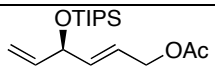
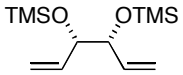
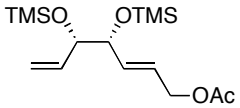
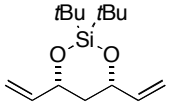
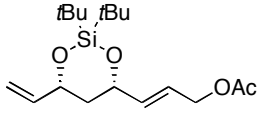
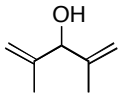
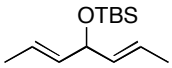
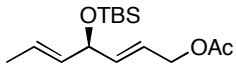


Catalyst	*ee*	Yield
2a	44%	20%
3a	22%	15%
4a	34%	20%
5a	44%	28%
6a	37%	12%

It was expected that use of an excess of **16**, which is more metathesis active than **15a**, would afford predominantly a ruthenium acetoxyethylidene as the propagating species. This was supported by the fact that the initial benzylidene of **2a** was observed to react exclusively with **16** to give cinnamyl acetate. Having controlled the propagating species, we achieved the first asymmetric olefin cross metathesis reaction, although these results are certainly unoptimized. The yields and *ee*'s were lower than expected. One systemic problem for the yield is that the terminal olefin present in the product is similar in reactivity to the starting material, resulting in consumption of the desired product and formation of a significant amount of symmetrical bis-cross product. Catalysts **2a** and **5a** emerged as the most enantioselective catalysts for this reaction. For catalysts **3a** - **6a,** as the meta substitution increased in size from a proton to a methyl group to an isopropyl group the enantioselectivity increased, but a *tert*-butyl group proved to be too large and eroded the enantioselectivity. However, moving the isopropyl group to the opposite meta position (**2a**) proved to be equally effective as **5a**. Since **5a** gave slightly better yield

than **2a,** we explored the use of **5a** with a number of other prochiral diene substrates (Table 4.4).

Table 4.4. ACM with *cis*-1,4-diacetoxy-2-butene using **5a**

Substrate	Product	*ee*	Yield
		52%	54%[a]
15b	**17b**		
		40%	17%[b]
18	**19**		
		37%	48%[c]
20	**21**		
	--	NR	NR
22			
		4%	23%[c]
23	**24**		

[a]5 mol% **5a**, 5 equiv of **15b** relative to **16**, neat, 40 °C, 6h.
[b]5 mol% **5a**, 5 equiv of **16**, neat, 40 °C, 6h.
[c]5 mol% **5a**, 5 equiv of **16**, 0.25 M in CH_2Cl_2, 40 °C, 6h.

Increasing the size of the protecting group by using TIPS protected 1,4-pentadiene-3-ol (**15b**, Table 2) resulted in a modest increase in *ee* from 44% to 52%. We also examined protected 1,2-diol **18** and protected 1,3-diol **20** that afforded *ee*'s similar to those obtained with **15a**. Attempting to improve the *ee* of ACM, we further reduced the

reactivity of the diene substrate by preparing both 1,1- and 1,2- disubstituted olefins. Unfortunately, diene **22** proved to be unreactive under these conditions and diene **23** gave only 4% *ee*. The poor result for **23** could result from the medium and large groups ($CHCHCH_3$and OTBS, respectively) becoming too similar in size. This initial report of ACM sets the stage for future catalyst and substrate design in order to make this transformation synthetically useful.

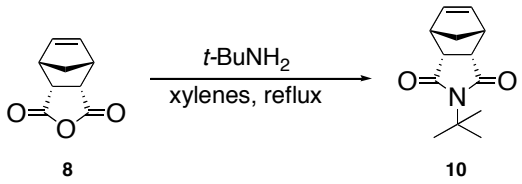
This chapter described an expansion in scope for asymmetric metathesis using highly active ruthenium catalysts with chiral monodentate NHCs. These catalysts showed excellent activity in ring-opening cross metathesis reactions and enantioselectivities ranged from 68% to 82%. These investigations allowed for the development of a working model for the mechanism of AROCM. In addition, the catalysts were used for the first asymmetric cross metathesis reactions and produced *ee*'s ranging from 37% to 52%. These reactions represent an important proof of principle and work is ongoing to improve the yields and enantioselectivities for ACM.

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 with reference to internal solvent for ^{1}H NMR and ^{13}C NMR spectra. Chemical shifts are reported in parts per million (ppm) downfield from H_3PO_4 for ^{31}P NMR spectra. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), septet (sept), multiplet (m), and broad (br). Optical rotations were taken on a Jasco P-1010 polarimeter with a

wavelength of 589 nm. The concentration "c" has units of g/100mL (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 stains, anisaldehyde or UV light. Flash column chromatography of organic compounds was performed using silica gel 60 (230-400 mesh), and flash column chromatography of ruthenium compounds was performed using silica gel 60 (230-400 mesh) from TSI Scientific (Cambridge, MA). All enantiomeric purities were determined by chiral GC (Chiraldex G-TA, 30m × 0.25mm or CP Chirasil-Dex-CB, 25m × 0.25mm) or chiral HPLC (Chiracel AD, OD-H, AS) 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, and $(PCy_3)_2Ru(=CHPh)Cl_2$ was a gift from Materia, Inc. Compounds **11**[10], **14**[11], **15a**[12], and **22**[13] are known compounds and were prepared as previously reported. Compounds **8**, **12**, and **13**, **16** were purchased from Aldrich and used as received.

Preparation of norbornene substrates

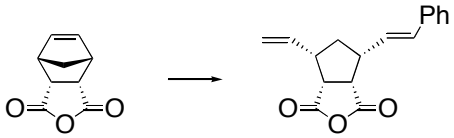


8 10

Imide 10. To a solution of anhydride **8** (71g, 430 mmol) in xylenes (400 mL) was added *tert*-butyl amine (50mL, 480 mmol). A Dean-Stark trap was attached and the reaction was stirred at reflux for 10 hours. At that point, 8 mL of H_2O had collected in the trap, so 350 mL of xylenes were distilled away. The reaction was cooled to RT and then placed in a 0 °C freezer but this did not induce crystallization. Instead, an excess of petroleum ether was added and the reaction was refluxed for 30 min. A minimal amount of MeOH was added and the reaction was refluxed for an additional 15 min. The flask was cooled to RT and then -78 °C. Imide **10** was obtained as white crystals (13.5 g, 14%). ^{1}H NMR (300 MHz, C_6D_6) δ 6.10 (t, J = 2.1 Hz, 2H), 3.35 - 3.32 (m, 2H), 3.08 - 3.07 (m, 2H), 1.66 (t, J = 1.8 Hz, 1H), 1.63 (t, J = 1.8 Hz, 1H), 1.45 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 179.3, 134.6, 58.3, 52.0, 45.6, 45.5, 28.7; HRMS (FAB+) calc for $C_{13}H_{17}NO_2$, 219.1259. Found 219.1263.

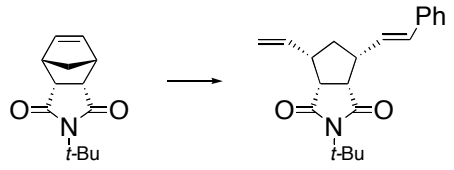
General Procedure A: asymmetric ring-opening cross metathesis reactions with 6a. To the norbornene (0.2 mmol) and styrene (230 μL, 2 mmol) in CH_2Cl_2 (3 mL) was added the dichloride catalyst **6a** (2.3 mg, 0.002 mmol) and the reaction stirred at RT for 1h. The solvent was evaporated, and the remaining residue was purified by flash chromatography to yield the desired functionalized cyclopentane.

General Procedure B: asymmetric ring-opening cross metathesis reactions with 6b. A solution of NaI (30 mg, 0.2 mmol) and dichloride catalyst **6a** (7 mg, 0.006 mmol) in CH_2Cl_2 (2 mL) was stirred at RT for 1 h. A solution of norbornene (0.2 mmol) and styrene (230 μL, 2 mmol) in CH_2Cl_2 (1 mL) was added, and the solution stirred at RT for 1 h. The solvent was evaporated, and the remaining residue was purified by flash chromatography to yield the desired functionalized cyclopentane.



8 **9**

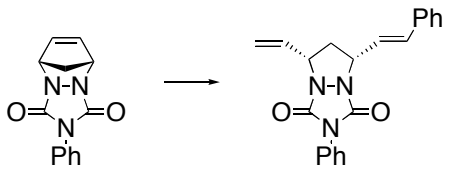
Anhydride 9. Using 33 mg of anhydride **8**, procedure A yielded 25 mg (47%) of anyhydride **9**. Procedure B at 0 °C yielded 26 mg (48%) of anhydride **9**. Column eluent was 50% Et_2O/Hexanes. The ee was determined by chiral HPLC (Chiralcel AS, 8% IPA/Hex, 0.75 mL/min, ret. times: 40.4 [major], 47.2 [minor]). Anhydride **9** is a known compound.[4d]



10 S4

Imide S4. Using 44 mg of imide **10**, procedure A yielded 37 mg (57%) of imide **S4** and 27 mg (42%) of *cis*-**S4**. Procedure B yielded 34 mg (52%) of **S4** and 2 mg (3%) of *cis*-**S4**. Column eluent was 30% Et_2O/Hexanes. The ee was determined by chiral HPLC (Chiralcel OD, 3% IPA/Hex, 1 mL/min, trans ret. times: 36.0 [major], 44.8 [minor]; cis

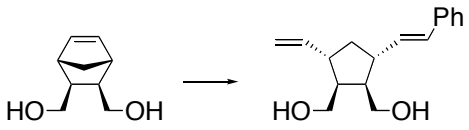
ret. times: 12.0 [minor], 13.6 [major]). Characterization of **S4** ^{1}H NMR (300 MHz, C_6D_6) δ 7.39-7.18 (m, 5H), 6.48-6.32 (m, 2H), 6.07-5.95 (m, 1H), 5.16-5.09 (m, 2H), 3.16-2.91 (m, 5H), 2.03-1.96 (m, 1H), 1.54 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 177.6, 137.5, 137.0, 130.7, 129.0, 128.8, 127.5, 126.6, 115.8, 58.6, 49.3, 48.9, 46.7, 45.9, 35.6, 28.7; HRMS (FAB+) calc for $C_{21}H_{25}NO_2$, 323.1885. Found 323.1895. Characterization of *cis*-**S4** ^{1}H NMR (300 MHz, C_6D_6) δ 7.37-7.23 (m, 5H), 6.65 (d, J = 11.1 Hz, 1H), 6.02-5.90 (m, 1H), 5.64 (dd, J = 11.7, 11.7 Hz, 1H), 5.12-5.04 (m, 2H), 3.37-3.25 (m, 1H), 3.10-3.01 (m, 2H), 2.90-2.79 (m, 1H), 1.94-1.86 (m, 1H), 1.59 (s, 9H).



11 **S5**

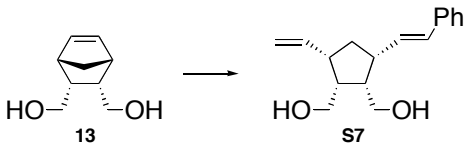
Heterocycle S5. Using 48 mg of heterocycle **11**, procedure A yielded 37 mg (54%) of **S5** and 32 mg (46%) of *cis*-**S5**. Procedure B yielded 37 mg (54%) of **S5** and 31 mg (45%) of *cis*-**S5**. Column eluent was 70% - 100% Et_2O/Hexanes. The ee for **S5** was determined by supercritical CO_2 chiral HPLC (Chiralcel OD-H, 5-25% MeOH over 10 min then 25% MeOH, 1 mL/min, ret. times: 11.8 [major], 14.0 [minor]). The ee for *cis*-**S5** was determined by chiral HPLC (Chiralcel AD, 8% IPA/Hexanes, 1mL/min, ret. times: 21.3 [minor], 33.0 [major]). Characterization of **S5** ^{1}H NMR (300 MHz, C_6D_6) δ 7.58-7.26 (m, 10H), 6.76 (d, J = 15.9 Hz, 1H), 6.25 (dd, J = 15.6, 6.6 Hz, 1H), 6.03-5.92 (m, 1H), 5.50 (dd, J = 18, 0.9 Hz, 1H), 5.34 (dd, J = 9, 0.9 Hz, 1H), 4.78 (dt, J = 6.9, 6.9 Hz, 1H), 4.63 (dt, J = 7.2, 7.2 Hz, 1H), 2.91-2.82 (m, 1H), 2.36-2.27 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 136.0, 135.1, 133.6, 129.3, 128.9 128.6, 127.0, 126.1, 125.6, 118.7, 59.7, 59.4, 41.9;

HRMS (FAB+) calc for $C_{21}H_{20}N_3O_2$, 346.1556. Found 346.1532. Characterization of *cis*-**S5** ^{1}H NMR (300 MHz, C_6D_6) δ 7.53-7.26 (m, 10H), 6.76 (d, J = 11.4 Hz, 1H), 5.97 (ddd, J = 16.8, 10.2, 6 Hz, 1H), 5.83 (dd, J = 11.7, 9.6 Hz, 1H), 5.50 (d, J = 9 Hz, 1H), 5.36 (d, J = 10.2 Hz, 1H), 5.02 (ddt, J = 8.1, 8.1, 0.9 Hz, 1H), 4.55 (dt, J = 6.9, 6.9 Hz, 1H), 2.80 (m, 1H), 2.27 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ 134.8, 133.4, 129.3, 129.0, 128.8, 128.7, 128.2, 127.9, 125.6, 118.8, 59.4, 55.4, 42.5; HRMS (FAB+) calc for $C_{21}H_{20}N_3O_2$, 346.1556. Found 346.1570.



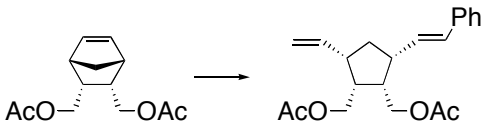
12 **S6**

Diol S6. Using 31 mg of diol **12**, procedure A yielded 8.5 mg (16%) of **S6** and 7.5 mg (14%) of *cis*-**S6**. Column eluent was 80% Et_2O/Hexanes. The ee was determined by chiral HPLC (Chiralcel OD, 5% IPA/Hex, 1mL/min, *cis*-**S6** ret. times: 11.7 [minor], 13.0 [major], **S6** ret. times: 18.8 [minor], 21.3 [major]). Diol **S6** is a known compound.[4c]



13 **S7**

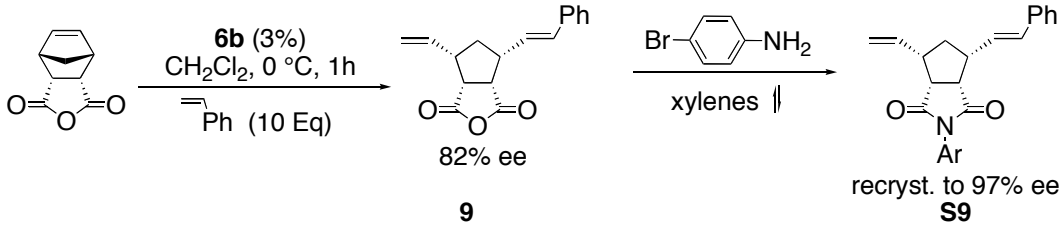
Diol S7. Using 31 mg of diol **13**, procedure A yielded 5 mg (10%) of an inseparable mixture of **S7** and *cis*-**S7**. Column eluent was 85% Et_2O/Hexanes. The ee was determined by chiral HPLC (Chiralcel OD, 5% IPA/Hex, 1mL/min, *cis*-**S7** ret. times: 15.4 [minor], 16.7 [major], **S7** ret. times: 22.3 [major], 27.2 [minor]). Diol **S7** is a known compound.[4c]



14 **S8**

Acetate protected diol S8. Using 49 mg of acetate protected diol **14**, procedure A yielded 62 mg (91%) of an inseparable mixture of **S8** and *cis*-**S8**. Procedure B yielded 53 mg (78%) of an inseparable mixture of **S8** and *cis*-**S8**. Column eluent was 30% Et_2O/Hexanes. The ee was determined by chiral HPLC (Chiralcel AD, 2% IPA/Hex, 1 mL/min, *cis*-**S8** ret. times: 10.3 [minor], 11.9 [major], **S8** ret. times: 16.0 [major], 18.6 [minor]). Characterization of a mixture of **S8** and *cis*-**S8** ^{1}H NMR (300 MHz, C_6D_6) δ 7.37 - 7. 18 (m, 5H, *cis* and *trans*), 6.49 (d, J = 11.7 Hz, 1H, *cis*), 6.40 (d, J = 15.6, 1H, *trans*), 6.22 - 6.14 (m, 1H, *cis* or *trans*), 5.89 - 5.76 (m, 1H, *cis* and *trans*), 5.60 (dd, J = 11.1, 11.1 Hz, 1H, *cis* or *trans*), 5.10 - 5.00 (m, 2H, *cis* and *trans*), 4.25 - 4.04 (m, 4H, *cis* and *trans*), 3.42 - 3.30 (m, 1H, *cis* or *trans*), 3.03 - 2.73 (m, 2H, *cis* and *trans*), 2.63 - 2.50 (m, 2H, *cis* and *trans*, 1H, *cis* or *trans*), 2.05 (s, 3H, *cis* and *trans*), 2.00 (s, 3H, *cis* or *trans*), 1.99 (s, 3H, *cis* or *trans*); ^{13}C (75 MHz, $CDCl_3$) δ 171.1, 171.1, 139.3, 139.0, 137.5, 133.4, 131.2, 131.1, 131.0, 130.3, 128.8, 128.5, 127.5, 127.1, 126.3, 116.0, 63.0, 62.9, 44.9, 44.8, 44.5, 44.4, 38.8, 36.7, 29.9, 21.3, 21.2 ; HRMS (FAB+) calc for $C_{21}H_{26}O_4$, 342.1831. Found 342.1839.

Absolute Stereochemistry Determination

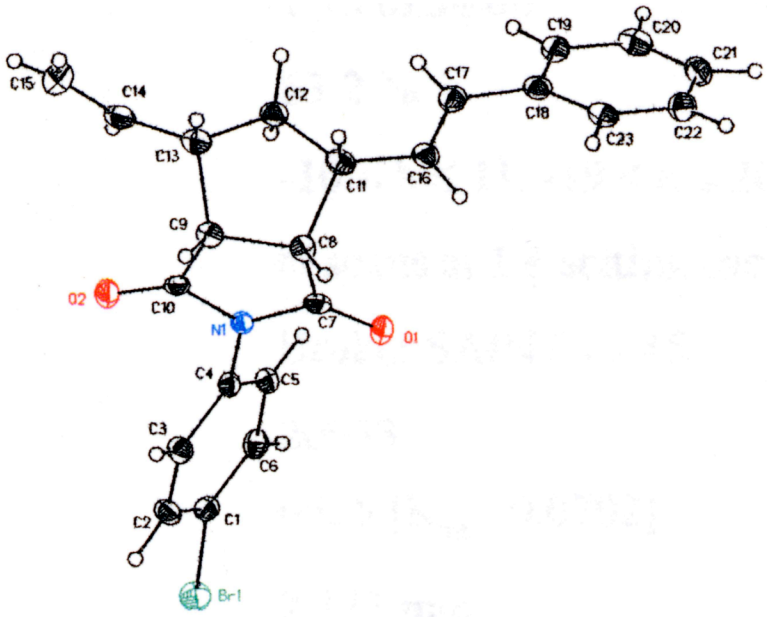


Using procedure B at 0 °C on a larger scale (607 mg, 3.7 mmol of norbornene starting material) yielded 258 mg (26%) of **9** in 82% ee. To this was added 4-bromoaniline (182 mg, 1.06 mmol) and xylenes (2 mL). The reaction was stirred at 140 °C for 24h, cooled

to RT and purified by flash column chromatography (50% Et_2O/Pentane) to yield **S9** (300 mg, 75%). Imide **S9** was recrystallized by slow diffusion of pentane into a solution of **S9** in benzene. The ee was determined by chiral HPLC (Chiralcel AD, 8% IPA/Hex, 1mL/min, ret. times: 31 [minor], 41 [major]). X-ray crystal analysis of three separate crystal samples revealed that the absolute stereochemistry was that which is depicted in the above scheme (all down).

In a separate experiment **9** (330 mg, 1.2 mmol) was treated with LAH (93 mg, 2.4 mmol) in Et_2O (14 mL) to give **S7** (146 mg, 47%). HPLC analysis confirmed that this sample had the same absolute stereochemistry as **S7** prepared from **13** using catalyst **6a**.

X-ray crystal analysis of S9



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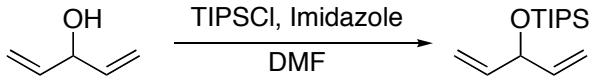
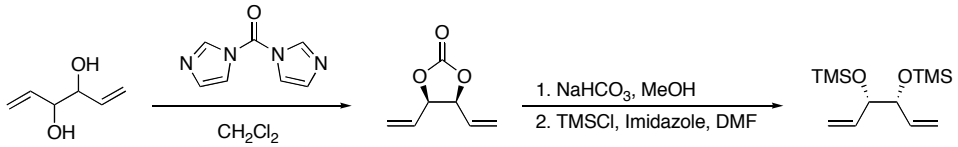
Cross Metathesis Substrate Preparation



15b

TIPS protected 1,4-pentadiene-3-ol (15b). TIPSCl (2.42 mL, 11.3 mmol) was added to a solution of 1,4-pentadiene-3-ol (1 mL, 10.3 mmol) and imidazole (770 mg, 11.3 mmol) in DMF (20 mL). The reaction was stirred overnight and then quenched with saturated aqueous NH_4Cl. Et_2O was added and the organic layer was removed. The aqueous layer was extracted 3x with Et_2O. The combined organic fractions were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic layer was then dried over $MgSO_4$, filtered, concentrated and purified by column chromatography (5% EtOAc/Hexanes) to yield 1.7 g (68%) of **15b**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddd, J = 17.1, 10.2, 5.4 Hz, 2H), 5.23 (ddd, J = 17.1, 1.5, 1.5 Hz, 2H), 5.07 (ddd, J = 10.2, 1.5, 1.5 Hz, 2H), 4.72-4.67 (m, 1H), 1.07-1.06 (m, 21H); ^{13}C (75 MHz, $CDCl_3$) δ 140.9, 113.9, 75.1, 18.3, 12.5; HRMS (EI+) calc for $C_{14}H_{28}OSi$, 240.1910. Found 240.1910.

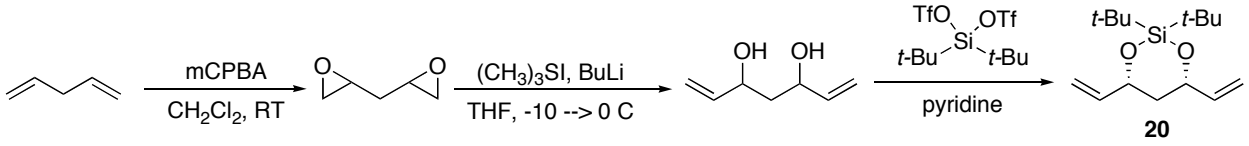


S10 **18**

TMS protected 1,5-hexadiene-3,4-diol 18. Carbonyl diimidazole (7.46 g, 46 mmol) was added to 1,5-hexadiene-3,4-diol (5 g, 43.8 mmol, mixture of *meso* and *rac*) in CH_2Cl_2 (60 mL). The reaction was stirred for 12h and quenched with saturated aqueous NH_4Cl. The aqueous layer was removed and the solution was concentrated. Et_2O and Hexanes were added and the aqueous layer was added. The solution was washed 3x with saturated aqueous NH_4Cl, dried over Na_2SO_4 and purified by flash column

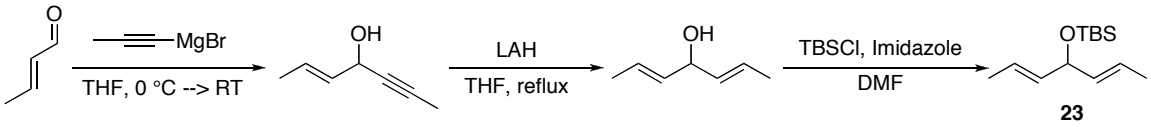
chromatography (40% Et_2O/Hex, desired spot is the lower spot) to yield 620 mg (10%) of carbonate protected *meso*-1,4-pentadiene-3-ol. To 550 mg (6.07 mmol) of this compound was added $NaHCO_3$ (1.5 g, 18.2 mmol) and methanol (10 mL). The reaction was stirred for 18h and then worked up to yield 690 mg (99%) of *meso*-1,5-hexadiene-3,4-diol (**S10)**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.94-5.83 (m, 2H), 5.39-5.26 (m, 4H), 4.22-4.19 (m, 2H), 2.19 (s, br, 2H); ^{13}C (75 MHz, $CDCl_3$) δ 136.1, 117.8, 75.6; HRMS (EI+) calc for $C_6H_{10}O_2$, 114.0681. Found 114.0683.

To **S10** (110 mg, 0.96 mmol) was added imidazole (328 mg, 4.8 mmol) and DMF (3mL). The reaction was cooled to 0 °C and TMSCl (306 μL, 2.4 mmol) was added. The reaction was stirred for 12h, during which time it warmed to RT, and Et_2O was added. The reaction was washed with saturated aqueous NH_4Cl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic layer was dried over Na_2SO_4 and purified by flash column chromatography (5% Et_2O/Hexanes) to yield **18** (137 mg, 55%). ^1H NMR (300 MHz, C_6D_6) δ 5.95-5.84 (m, 2H), 5.21 (dd, J = 18.3, 1.2 Hz, 2H), 5.13 (ddd, J = 10.5, 1.2, 1.2 Hz, 2H), 3.96-3.94 (m, 2H), 0.10 (s, 18H). ^{13}C (75 MHz, $CDCl_3$) δ 138.6, 115.7, 76.8, 0.5; HRMS (EI+) calc for $C_{12}H_{25}O_2Si_2$, 257.1393. Found 257.1400.



Protected 1,3-diol 20. Following literature procedure,[14] 1,6-heptadiene-3,5-diol was prepared as a mixture of *meso* and *rac* isomers. To this diol mixture (815 mg, 6.36 mmol) in pyridine (20 mL) was added di-*tert*-butylsilylbis(trifluoromethanesulfonate)

(2.55 ml, 6.99 mmol). The reaction was stirred at rt for 3 hours and Et_2O was added. The reaction was washed 3x with saturated aqueous NH_4Cl, dried over $MgSO_4$, concentrated and purified by flash column chromatography (3% Et_2O/Hexanes) to yield 633mg (37%) of **20**. ^1H NMR (300 MHz, C_6D_6) δ 5.84 (ddd, J = 6.0, 12.0, 18.0 Hz, 2H), 5.33 (ddd, J = 2.0, 2.0, 24 Hz, 2H), 5.08 (ddd, J = 2.0, 2.0, 9.0 Hz, 2H), 4.64-4.57 (m, 2H), 1.8-1.7 (m, 1H), 1.6-1.5 (m, 1H), 1.1 (s, 9H), 1.0 (s, 9H).

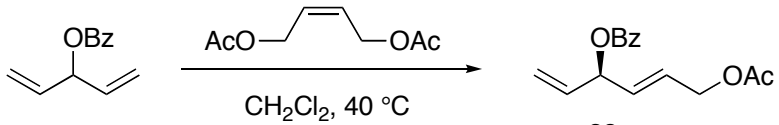


23

TBS protected alcohol 23. A modified literature procedure was used.[15] To a solution of 1-propynlmagnesiumbromide in THF (100 mL, 0.5 M, 50 mmol) at 0 °C was added crotonaldehyde (3.5 mL, 42.2 mmol). The reaction was stirred for 12 hours and allowed to warm to RT during this time. Saturated aqueous NH_4Cl was added and the reaction was extracted 3x with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$ and purified by flash column chromatography (20% EtOAc/Hexanes) to yield 4.18 g (88%) of the propargyl alcohol. This propargyl alcohol (4.18 g, 37.3 mmol) in THF (80 mL) was added to LAH (2.83 g, 74.5 mmol) in THF (250 mL) at 0 °C. The reaction was warmed to rt and then stirred at reflux for 18 hours. The reaction was quenched with H_2O and 15% aqueous solution of NaOH, filtered through celite and purified by flash column chromatography (20% EtOAc/Hexanes) to yield 1.16 g (27%) of the symmetrical alcohol. A number of mixed fractions were recolumned in 5% EtOAc/Hexanes to yield an additional 0.815 g (19%) of the symmetrical alcohol. To this alcohol (.815 g, 7.1 mmol) was added DMF (15mL), imidazole (483 mg, 7.1 mmol) and TBSCl (1.07 g, 7.1 mmol). The reaction was stirred for 12 hours and saturated

aqueous NH_4Cl was added. The mixture was extracted 3x with Et_2O, dried over $MgSO_4$ and purified by flash column chromatography (5% Et_2O/Hexanes) to yield 1.184 g (74%) of **23**. ^1H NMR (300 MHz, $CDCl_3$) δ 5.64-5.53 (m, 2H), 5.43 (ddq, J = 1.2, 5.7, 15.0 Hz, 2H), 4.53-4.49 (m, 1H), 1.68 (dd, J = 1.2, 6.6 Hz. 6H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C (75 MHz, $CDCl_3$) δ 134.1, 125.0, 74.2, 26.2, 18.6, 17.9, -4.3; HRMS (EI+) calc for $C_{13}H_{26}OSi$, 226.1753, found 226.1755.

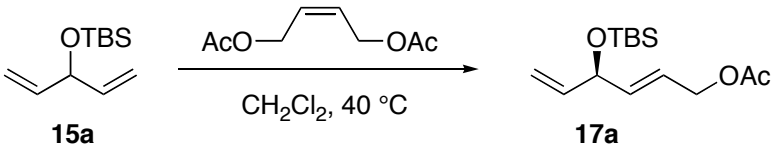
Asymmetric Cross Metathesis Reactions



28

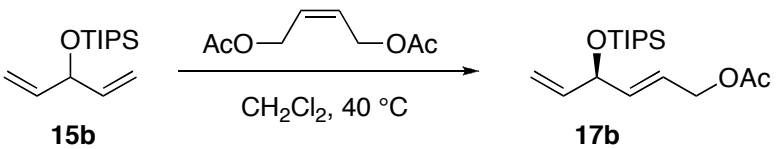
Diene 28. Benzoate protected 1,4-pentadiene-3-ol (32 mg, 0.17 mmol) was added to *cis*-1,4-diacetoxy-2-butene (134 μL, 0.85 mmol) in CH_2Cl_2 (570 μL) open to air. The flask was then flushed with argon and catalyst **5a** (9 mg, 0.0085 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C overnight (12h). The reaction was concentrated and purified by column chromatography in 20% Et_2O/Hexanes to yield (17 mg, 38%) of the desired product. When a TLC plate is stained with anisaldehyde, the product is purple, the starting material is black and *cis*-1,4-diacetoxy-2-butene is brown. The enantiomeric excess was determined by chiral HPLC analysis (Chiralcel AD, 1% IPA/Hex, 1 mL/min, ret. times: 13.8 [major], 15.5 [minor]). ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 7.2 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.44 (t, J = 7.2 Hz,

2H), 5.99-5.89 (m, 4H), 5.40 (d, J = 16.5 Hz, 1H), 5.29 (d, J = 9.9 Hz, 1H), 4.60 (d, J = 3.9 Hz, 2H), 2.07 (3H, s); ^{13}C (75 MHz, $CDCl_3$) δ 170.9, 165.6, 135.0, 133.3, 131.0, 130.4, 129.9, 128.6, 127.6, 118.1, 74.6, 64.1, 21.1; HRMS (EI+) calc for $C_{15}H_{16}O_4$, 260.1049. Found 260.1057.



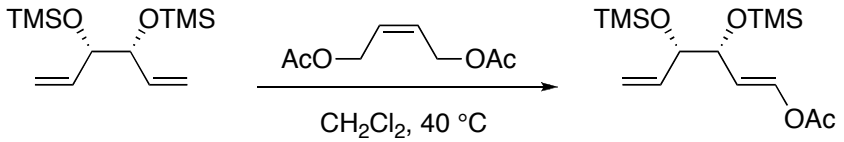
15a **17a**

Diene 17a. Substrate **15a** (37 mg, 0.186 mmol) was added to *cis*-1,4-diacetoxy-2-butene (147 μL, 0.93 mmol) in CH_2Cl_2 (570 μL) open to air. The flask was then flushed with argon and catalyst **5a** (9.3 mg, 0.0093 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C overnight (12h). The reaction was purified by column chromatography in 20% Et_2O/Hexanes to yield (14 mg, 28%) of the desired product. To determine the enantiomeric excess, **17a** was converted to **28**. NEt_3-3HF (50 μL) was added to **17a** in CH_2Cl_2 (1 mL); the reaction was stirred for 12h. Then, NEt_3 (200 μL) and benzoyl chloride (50 μL) were added and the reaction was stirred for 2h. Workup and analysis was the same as for **28**. Characterization of **17a** ^{1}H NMR (300 MHz, C_6D_6) δ 5.84-5.73 (m, 3H), 5.22 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 5.07 (ddd, J = 10.2, 1.5, 1.5 Hz, 1H), 4.64-4.62 (m, 1H), 5.56 (dd, J = 3.9, 0.6 Hz, 2H), 2.06 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H). ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 139.9, 136.6, 123.6, 114.4, 73.7, 64.6, 26.1, 21.1, 18.6, -4.5, -4.5; HRMS (EI+) calc for $C_{14}H_{25}O_3Si$, 269.1573. Found 269.1561.



15b **17b**

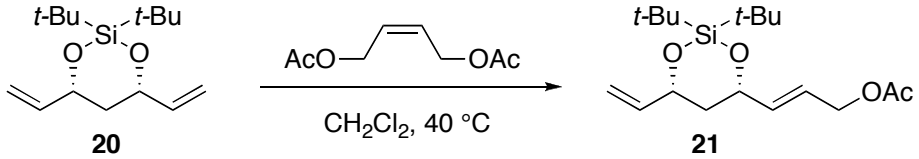
Diene 17b. Substrate **15b** (44.8 mg, 0.186 mmol) was added to *cis*-1,4-diacetoxy-2-butene (147 μL, 0.93 mmol) open to air. The flask was then flushed with argon and catalyst **5a** (9.3 mg, 0.0093 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C overnight (12h). The reaction was purified by column chromatography in 20% Et_2O/Hexanes to yield (5 mg, 8%) of the desired product. To determine the enantiomeric excess, **17b** was converted to **28**. NEt_3-3HF (50 μL) was added to **17b** in CH_2Cl_2 (1 mL); the reaction was stirred for 12h. Then, NEt_3 (200 μL) and benzoyl chloride (50 μL) were added and the reaction was stirred for 2h. Workup and analysis was the same as for **28**. Characterization of **17b** ^{1}H NMR (300 MHz, C_6D_6) δ 5.85-5.74 (m, 3H), 5.23 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 5.08 (ddd, J = 10.2, 1.5, 1.5 Hz, 1H), 4.73-4.70 (m, 1H), 4.56 (d, J = 4.2 Hz, 2H), 2.05 (s, 3H), 1.06-1.04 (m, 21H). ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 140.4, 137.2, 123.5, 114.2, 73.9, 64.6, 21.2, 18.2, 12.5; HRMS (EI+) calc for $C_{17}H_{33}O_3Si$, 313.2199. Found 313.2184.



18 **19**

Diene 19. Substrate **18** (27 mg, 0.104 mmol) was added to *cis*-1,4-diacetoxy-2-butene (82 μL, 0.52 mmol) open to air. The flask was then flushed with argon and catalyst **5a** (5.7 mg, 0.0052 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C for 12h. The reaction was purified by column chromatography in 40% Et_2O/Hexanes to yield (6 mg, 17%) of **19**. For ee determination, **19** was converted into its triacetate analogue. TMS protected diol **19** (6 mg) in CH_2Cl_2 (.5 mL) was treated

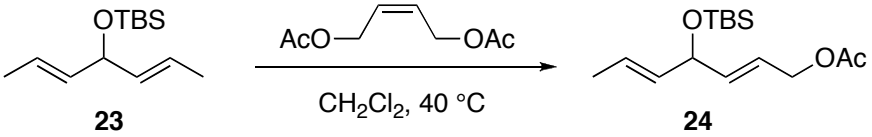
with NEt_3-3HF (3 drops) and stirred for 0.5 hours. Triethyl amine (100 μL) and Ac_2O (50 μL) were added and the reaction was stirred for 14 hours. This crude sample was then directly analyzed by chiral GC (β-DM, 100 °C for 5 min, then ramp 2°C/min to 200 °C, ret. times: 30.7 [minor], 30.9 [major]). Characterization of **19** ^{1}H NMR (300 MHz, C_6D_6) δ 5.93-5.71 (m, 3H), 5.21 (ddd, J = 17.1, 1.5, 1.5 Hz, 1H), 5.15-5.11 (m, 1H), 4.56 (d, J = 5.4 Hz, 2H), 3.99-3.91 (m, 1H), 2.06 (s, 3H), 0.09 (18H). ^{13}C (75 MHz, $CDCl_3$) δ 138.5, 135.2, 125.2, 115.9, 77.4, 76.3, 64.6, 21.2, 0.5, 0.5; HRMS (EI+) calc for $C_{15}H_{31}O_4Si_2$, 331.1761. Found 331.1769.



20 **21**

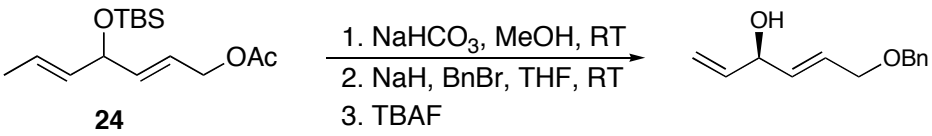
Diene 21. Substrate **20** (33 mg, 0.124 mmol) was added to *cis*-1,4-diacetoxy-2-butene (59 μL, 0.37 mmol) in CH_2Cl_2 (570 μL) open to air. The flask was then flushed with argon and catalyst **5a** (6.7 mg, 0.0062 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C for 12h. The reaction was purified by flash column chromatography (10% Et_2O/Hexanes) to yield (20 mg, 48%) of **21**. For ee analysis the diol was reprotected with benzoate groups. Silyl protected diol **21** (20 mg) in CH_2Cl_2 (1mL) was treated with NEt_3-3HF (100 μL) and stirred for 18 hours. Triethyl amine (300 μL) and BzCl (100 μL) were added and the reaction was stirred for 14 hours. The benzoate-protected diol was purified by flash column chromatography (40% Et_2O/Hexanes) and analyzed by chiral HPLC (Chiralcel AD, 5% EtOH/Hexanes, 1mL/min, ret. times: 16.2 [major], 19.4 [minor]). Characterization for **21** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91-5.70 (m, 3H), 5.32 (d, J = 18 Hz, 1H), 5.08 (d, J = 9 Hz, 1H), 4.66-

4.56 (m, 4H), 2.08 (s, 3H), 1.74 (d, J = 15 Hz, 1H), 1.57 (s, 1H), 1.05 (s, 9H), 1.02 (s, 9H).



23 **24**

Diene 24. Substrate **23** (98 μL, 0.5 mmol) was added to *cis*-1,4-diacetoxy-2-butene (79 μL, 0.5 mmol) in CH_2Cl_2 (1 mL) open to air. The flask was then flushed with argon and catalyst **5a** (6.7 mg, 0.0062 mmol) was added. A reflux condenser was attached and the reaction was stirred at 40 °C for 12h. The reaction was purified by flash column chromatography (10% Et_2O/Hexanes) to yield (32 mg, 23%) of **24**. For ee analysis a three step sequence was carried out (see below). Characterization of **24** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74-5.72 (m, 2H), 5.67-5.55 (m, 1H), 5.45-5.36 (m, 1H), 4.59-4.48 (m, 3H), 2.06 (s, 3H), 1.68 (d, 6.3 Hz, 3H), 0.90 (s, 9H), 0.05 (s, 6H). ^{13}C (75 MHz, $CDCl_3$) δ 171.0, 137.4, 133.1, 126.0, 123.1, 73.4, 64.7, 26.1, 21.2, 17.9, -4.3, -4.5; HRMS (EI+) calc for $C_{15}H_{27}O_3Si$, 283.1730. Found 283.1741.



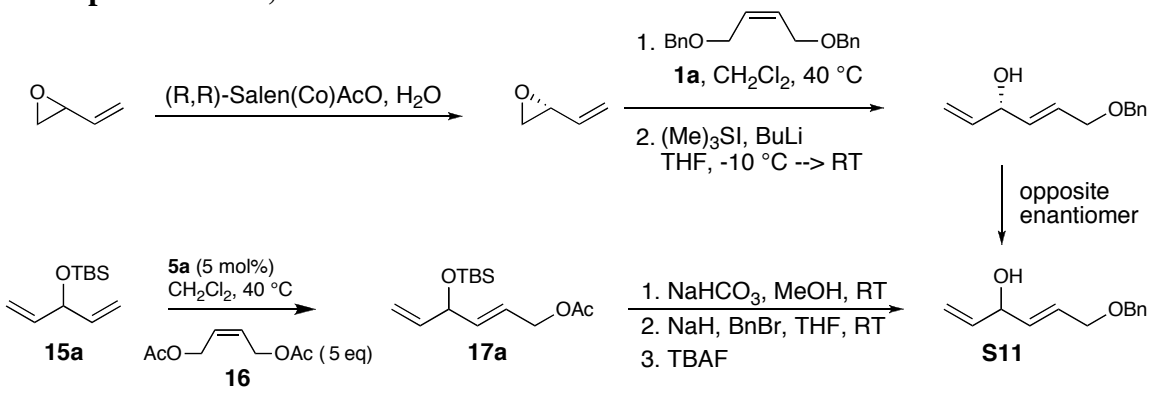
24

MeOH (1 mL) and $NaHCO_3$ (75 mg, 0.89 mmol) were added to **24** (32 mg, 0.14). The reaction was stirred for 12 hours and H_2O and Et_2O were added. The Et_2O was removed and the remaining mixture was extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$, filtered and concentrated to yield 26 mg (96%) of the deprotected primary alcohol. To this compound (26 mg, 0.11 mmol) was added THF (3 mL) and NaH (85 mg, 0.22 mmol) and the reaction was stirred for 20 minutes. Benzyl bromide was purified by passing it through neutral alumina and 38 μL (.33 mmol) was

added. The reaction was stirred for 12 hours and then purified by flash column chromatography (10% Et_2O/hexanes) to yield 23 mg (65%) of the protected diol. To this compound (23 mg, 0.07 mmol) was added TBAF (150 μL, 1M in THF). The reaction was stirred for 2 hours and Et_2O and saturated aqueous NH_4Cl were added. The Et_2O was removed and the aqueous layer was extracted with Et_2O. The combined ether layers were washed with $NaHCO_3$, dried over $MgSO_4$ and purified by flash column chromatography (50% Et_2O/hexanes) to yield 10 mg (64%) of the deprotected secondary alcohol. The ee was determined by chiral HPLC (Chiralcel OD, 0.75% IPA/hexanes, 1mL/min, ret. times: 94.6 [major], 116.4 [minor]).

Cross Metathesis Stereoproofs

Stereoproof for 17a,b.

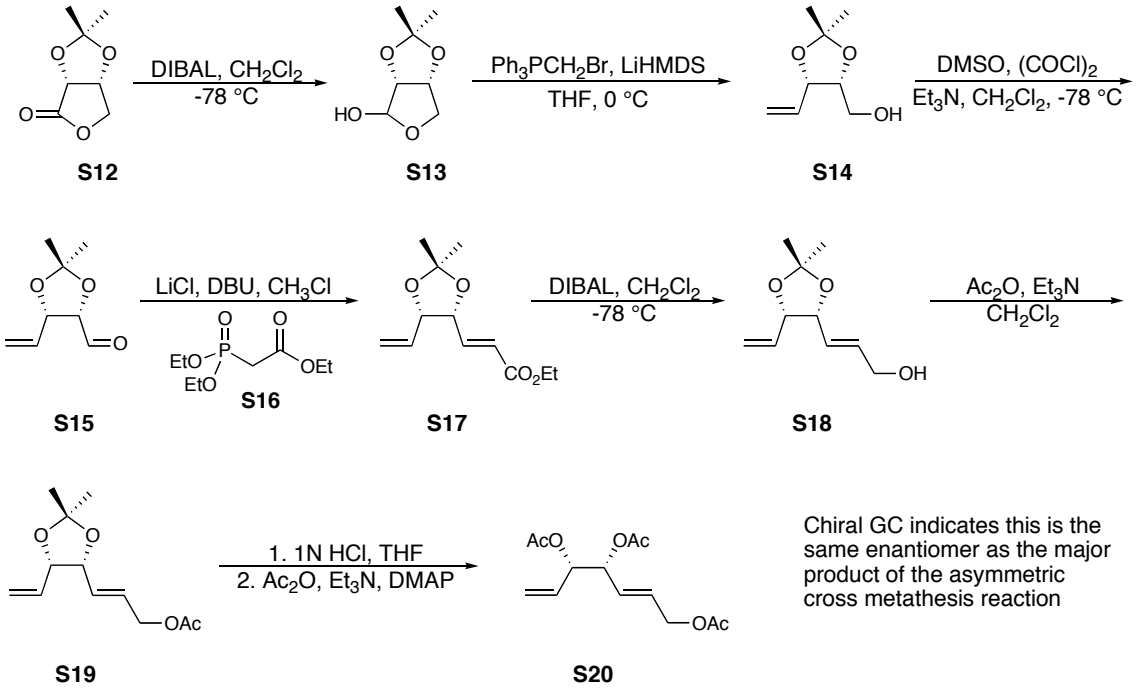


To prepare a known sample: (R,R)-Salen(Co) (562 mg, 0.93 mmol) was stirred with glacial acetic acid (600 μL) in toluene (5 mL) for 30 minutes. Then the solution was concentrated to dryness and butadiene monoxide (5mL, 62 mmol) was added. The solution was cooled to 0 °C and H_2O (782 μL, 43.4 mmol) was added. The reaction was stirred for 72 hours and during this period it was allowed to warm to rt. The epoxide was isolated by vacuum transfer to a receiving flask cooled to -78 °C. The epoxide was put through a plug of alumina to dry it and the epoxide (626 mg, 29%) was isolate enantioenriched $[\alpha]^{22}_{D}$ -9.93 (c 3.17, *i*PrOH) [Lit. value: -10.4, c 2.97, *i*PrOH]. In a second step, catalyst **1a** (42 mg, 0.05 mmol) was added to the enantioenriched epoxide (322 μL, 4 mmol) and *cis*-1,4-dibenzyloxy-2-butene (257 μL, 1 mmol) in CH_2Cl_2 (5 mL). The reaction was stirred for 12 hours at 40 °C, then cooled to rt, concentrated and purified by column chromatography (15% Et_2O/hexanes, the product is the middle spot) to give the desired product (121 mg, 63%). This product was added to a solution of $(Me)_3SI$ (344 mg, 1.68 mmol) and BuLi (980 μL, 1.57 mmol) which was prestirred for 2.5 hours at -10 °C. The reaction was stirred for 12 hours during which time it was allowed to warm to rt and then the reaction was quenched with a saturated aqueous

solution of NH_4Cl. Et_2O was added and the organic layer was removed, the aqueous layer was extracted 3x with CH_2Cl_2 and the combined organic fractions were dried over $MgSO_4$, concentrated and purified by column chromatography (30% Et_2O/Hex) to yield **S11** (65 mg, 57%). The material was analyzed by chiral HPLC (Chiralcel OD, 206 nm, 2% IPA/Hex, 1mL/min) to give a minor peak at 35.6 min and a major peak at 41.1 min with an ee of 44%.

To prepare a sample by asymmetric cross metathesis: **17a** was prepared as previously described. An excess of $NaHCO_3$ (93 mg, 1.1 mmol) and MeOH (3 mL) was added to **17a** (26 mg, 0.1 mmol). The reaction was stirred for 48 hours and then H_2O and Et_2O were added. The ether was separated and the aqueous layer was extracted 3x with ether. The organic fractions were combined and dried over $MgSO_4$ and concentrated to give the desired primary alcohol (23 mg, 99%). In a second step, BnBr (36 μL, 0.3 mmol) was added to the primary alcohol (23 mg, 0.1 mmol) and NaH (6 mg, 0.15 mmol) prestirred for 15 minutes in THF (500 μL). The reaction was stirred for 48 hours and then purified by column chromatography (5% Et_2O/Hex) to give the TBS and Bn protected diol (25 mg, 78%). To this substrate (25 mg, 0.078 mmol) was added TBAF (200 μΛ, 1M in THF, 0.2 mmol). The reaction was stirred for 12 hours and then quenched with a saturated aqueous solution of NH_4Cl. The reaction was extracted 3 times with diethyl ether. The combined organic fractions were dried over $MgSO_4$ and purified by column chromatography (50% Et_2O/Hex) to give **S11** (6 mg, 38%). This sample was also analyzed by chiral HPLC (Chiralcel OD, 206 nm, 2% IPA/Hex, 1mL/min) to give a major peak at 36.2 min and a minor peak at 42.0 min with an ee of 44%.

Stereoproof of 19



Compound **S12** was purchased *enantiopure* from Aldrich. In CH_2Cl_2 (180 mL), **S12** (5.7 g, 36 mmol) was cooled to -78 °C and DIBAL (41.1 mL, 1M in Toluene, 41.1 mmol) was added. The reaction was stirred for 3 hours and MeOH (12 mL) was added along with H_2O (100 mL) and Na_2Tartrate-$(H_2O)_4$. The reaction was stirred for 12 hours and the aqueous layer was removed; the organic layer was washed with 1N HCl. The combined aqueous layers were extracted 3x with EtOAc. The combined organic layers were dried over $MgSO_4$ and purified by flash column chromatography (2% EtOAc/Hex) to yield 5 g (87%) of **S13**.

Ph_3PCH_2Br (4.91 g, 13.7 mmol) in THF (50 mL) was cooled to 0 °C and LiHMDS (27.4 mL, 1M in THF, 27.4 mmol) was added. Lactol **S13** (2 g, 12.5 mmol) was added via canula in THF (15 mL). The reaction was stirred for 14 hours. Et_2O (50 mL) and a saturated aqueous solution of NH_4Cl (100 mL) were added, the Et_2O was separated and

the aqueous layer was extracted 2x with Et_2O. The combined organic layers were dried over Na_2SO_4 and purified by flash column chromatography (20% EtOAc/CH_2Cl_2) to yield 1.98 g (99%) of **S14**.

CH_2Cl_2 (10 mL) was cooled to -78 °C and $(COCl)_2$ (276 μL, 3.16 mmol) was added. DMSO (450 μL, 6.32 mmol) was added slowly and gas was evolved. The reaction was stirred 10 minutes and **S14** (250 mg, 1.58 mmol) in CH_2Cl_2 (5 mL) was added via canula. The reaction was stirred for 1 hour and triethylamine was added dropwise. The reaction was stirred for 30 minutes and warmed to rt. Et_2O, hexanes and a saturated aqueous solution of NH_4Cl were added, the Et_2O was removed and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were dried over Na_2SO_4 to yield **S15**. This product was taken on crude. To **S15** (1.58 mmol estimated) was added flame dried LiCl (80.5 mg, 1.9 mmol) and CH_3CN (10 mL). To the solution was added **S16** (377 μL, 1.90 mmol) and DBU (236 μL, 1.58 mmol). The reaction was stirred 30 minutes, worked up and purified by flash column chromatography (50% EtOAc/Hexanes) to yield 64 mg (18%) of **S17**.

To **S17** (54 mg, 0.284 mmol) in toluene (1 mL) at 0 °C was added DIBAL (711 μL, 1M in toluene, 0.711 mmol). The reaction was stirred for 2 hours and slowly warmed to RT, quenched with a saturated aqueous solution of $NaHCO_3$ and stirred vigorously. The reaction was extracted 3x with toluene, dried and purified by flash column chromatography (60% Et_2O/hexanes) to yield 33 mg (75%) of **S18**.

CH_2Cl_2 (1 mL), triethylamine (100 μL) and Ac_2O (50 μL) were added to **S18** (33 mg) and the reaction was stirred for 2 hours. Et_2O, hexanes and a saturated solution of NH_4Cl were added, the Et_2O was removed and the aqueous layer was extracted 2x with Et_2O. The combined organic layers were dried over Na_2SO_4 and purified by flash column chromatography (30% Et_2O/hexanes) to yield 36 mg (89%) of **S19**.

To **S19** (36 mg) in CH_2Cl_2 (1 mL) was added 1N HCl (100 μL). The reaction was stirred for 12 hours and then MeOH was added. The reaction was stirred 8 hours and then neutralized. The reaction was extracted 3x with Et_2O and dried over Na_2SO_4, filtered and concentrated. To this was added CH_2Cl_2, Ac_2O and triethylamine and DMAP. The reaction was worked up and purified by flash column chromatography (40% Et_2O/hexanes) to yield **S20**.

Chiral GC analysis (β-DM, 100 °C for 5 min, then ramp 2°C/min to 200 °C, ret. time: 30.9) demonstrated that this was the same enantiomer as the major enantiomer produced by the asymmetric cross metathesis of **18**.

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[7] The absolute stereochemistry of **9** has been determined by X-ray crystal structure analysis of an imide derivative (See Experimental). Based on a comparison of HPLC traces run under identical conditions, our stereoproof indicates that the incorrect absolute stereoisomer was reported in ref. 4d.

[8] For example, see: Brown, H. C.; Ayyangar, N. R.; Zweifel, G. *J. Am. Chem. Soc.* **1964**, *86*, 397.

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