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Stereoselective Synthesis of Pyrans from Epoxyalkenes: Dual Catalysis with Palladium and Brønsted Acid

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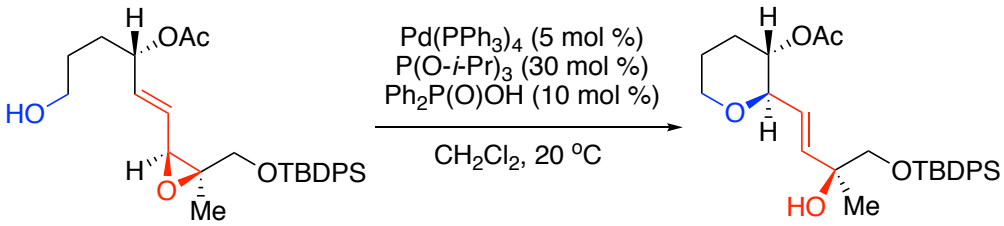


ABSTRACT: We describe regio- and stereoselective cycloisomerizations of alcohols tethered to epoxyalkenes, to construct alkene-substituted pyrans. These transformations are best catalyzed by $Pd(PPh_3)_4$ in the presence of phosphite ligands, and with diphenylphosphinic acid as an essential Brønsted acid co-catalyst for activation of the epoxyalkene.

INTRODUCTION

The stereoselective synthesis of cyclic ethers has been a long-standing interest of our laboratory.[1] As a new strategy for the synthesis of polycyclic ethers, we considered regioselective and stereospecific cycloisomerizations of epoxyalkenes to form highly functionalized pyrans. In this approach, the pendant hydroxyl group of **1** would undergo vinylogous addition onto the alkene terminus of an epoxyalkene, with the stereochemical information of the epoxide transferred to the new chiral center formed in the pyran **2** (Figure 1). Our goal was the stereocontrolled synthesis of the three chiral centers of compound **2**, corresponding to several natural product substructures **3**, including yessotoxin (R_1=Me) and gambierol (R_1=H).[2]

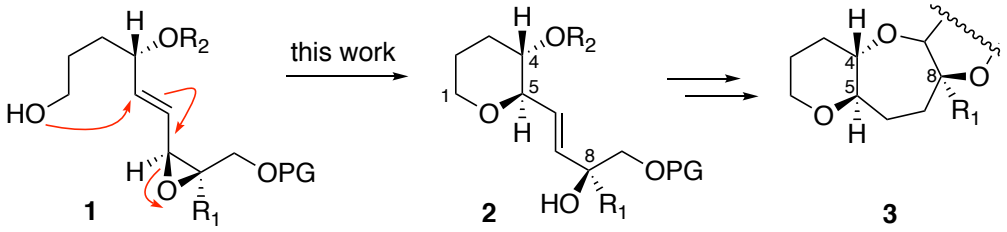
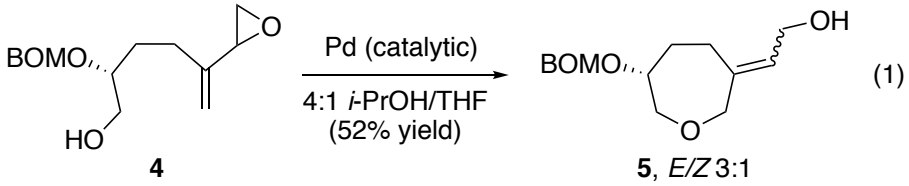


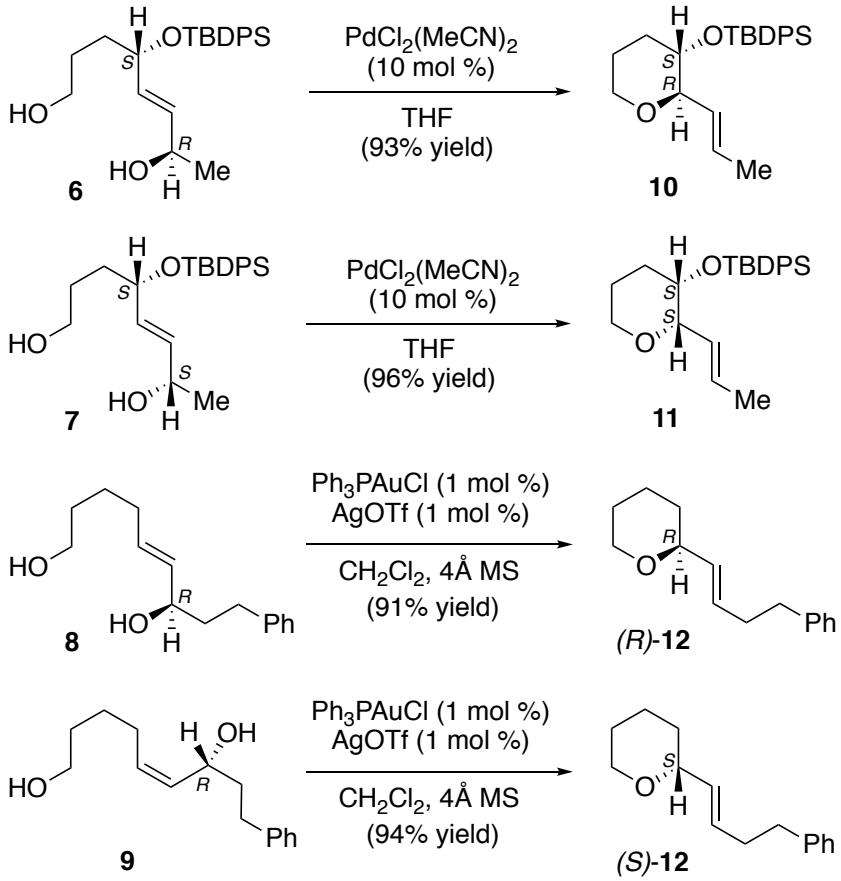
Figure 1. Proposed stereoselective synthesis of a substructure **2** commonly found in fused polycyclic ether natural products

Despite the straightforward nature of the proposed transformation **1** → **2** (Figure 1), the literature has provided very few examples *in which an alcohol has added to the alkene terminus of an epoxyalkene*.[3] Trost reported a single example of a Pd-catalyzed oxacyclization of such a substrate, converting epoxyalkene **4** into the oxepane isomer **5**, arising from regioselective addition to the alkene terminus (eq 1).[4]



4 **5**, *E/Z* 3:1

More recently, Uenishi has described Pd-catalyzed dehydrative oxacyclizations of allylic alcohols **6** and **7** with tethered hydroxyl groups, observing stereospecificity in the formation of the pyrans **10** and **11** corresponding to the stereochemistry of the allylic alcohols (Figure 2).[5] Aponick has subsequently demonstrated stereospecific Au-catalyzed cyclizations of *trans*-**8** and *cis*-**9** to the respective enantiomers of pyran **12**.[6]



6 **10**

7 **11**

8 *(R)*-**12**

9 *(S)*-**12**

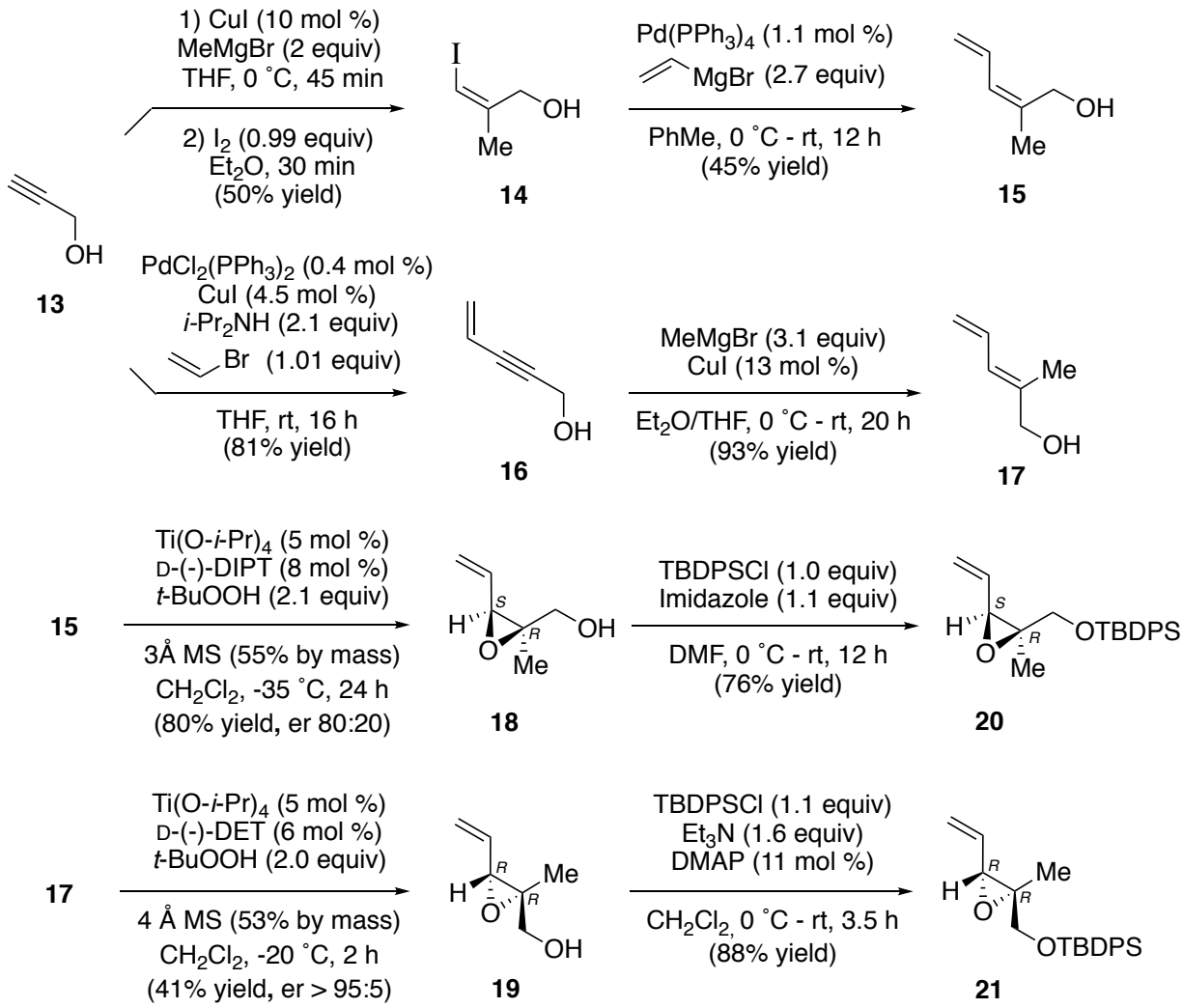
Figure 2. Intramolecular additions of alcohols tethered to allylic alcohols, with stereospecificity corresponding to alcohol and alkene stereochemistry of substrates **6** - **9**

In this Article, we describe the development of a catalytic process for stereoselective cycloisomerizations of epoxyalkenes **1** into cyclic ethers **2**.

RESULTS AND DISCUSSION

Stereoselective preparations of epoxyalkenes tethered to hydroxyl groups: Each substrate in this study was synthesized by a cross-metathesis strategy. The epoxyalkene diastereomers **20** or **21** were obtained from the corresponding *Z*- or *E*-dienyl alcohols **15** or **17** (Scheme 1). Specifically, Cu-catalyzed carbomagnesiation of propargyl alcohol (**13**) with methylmagnesium bromide followed by quenching with elemental iodine provided (*Z*)-3-iodo-2-methylprop-2-en-1-ol (**14**),[7,8] and subsequent Pd-catalyzed Kumada coupling with vinylmagnesium bromide gave (*Z*)-2-methyl-2,4-pentadien-1-ol (**15**).[9,10] A complementary sequence of steps, namely Sonogashira coupling of propargyl alcohol and vinyl bromide to pent-4-en-2-yn-1-ol (**16**),[11] followed by Cu-catalyzed carbomagnesiation yielded exclusively (*E*)-2-methyl-2,4-pentadien-1-ol (**17**).[12,13] Sharpless asymmetric epoxidation of each dienyl alcohol **15** or **17** provided the corresponding epoxyalkenyl alcohols **18** or **19**.[14] The primary alcohols were then blocked as TBDPS ethers, completing the synthesis of epoxyalkene diastereomers **20** and **21**.

Scheme 1. Stereoselective syntheses of epoxyalkenes **20** and **21**



For the other alkene components, trimethylsilyl ethers **22** - **24** (Figure 3) were prepared from the corresponding alkenyl alcohols,[15] using hexamethyldisilazane and catalytic *N*-bromosuccinimide, under conditions that did not require aqueous workup.[16] For the differentially *O*-protected alkenyl diol synthon **28** (Scheme 2), enzyme-catalyzed resolution of the racemic allylic alcohol **25**[17] in the presence of isopropenyl acetate[18] provided a separable mixture of the (*S*)-acetate **26** and recovered (*R*)-**25**. Chemoselective deprotection of the TBS ether afforded primary alcohol **27**, which was reprotected as the more labile TMS ether **28**.

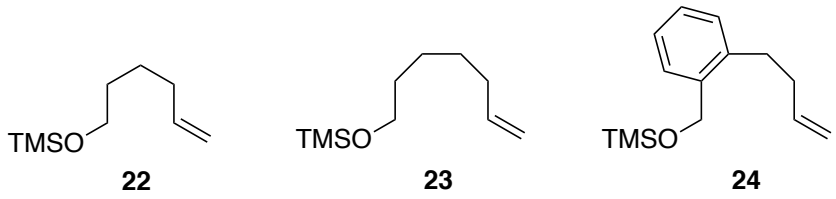
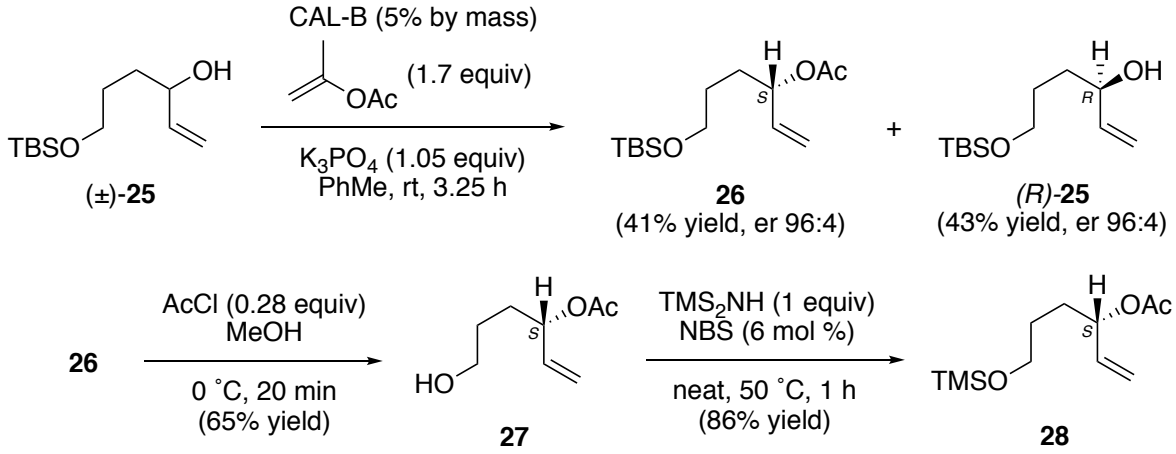
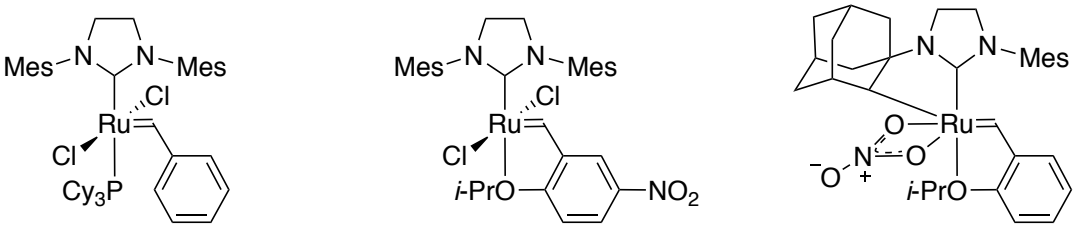


Figure 3. Structures of *O*-trimethylsilyl ethers **22** - **24** from alkenyl alcohols

Scheme 2. Kinetic resolution of racemic **25**, forming differentially *O*-protected **28**



Cross-metathesis experiments with the epoxyalkene **20** were initially conducted with the TBS-ether-alkene **26**, catalyzed by Grubbs II catalyst[19] (**29**, Figure 4). However, the TBS ether of the product was difficult to remove due to side-reactions of the epoxyalkene, and metathesis reactions proceeded with poor yields with the primary alcohol **27**. Therefore, the labile TMS-ether-alkenes **22** - **24** and **28** were preferred. The nitro-substituted Grela metathesis catalyst (**30**)[20] generally gave the best *trans*-selectivity with relatively low catalyst loading. Typically, a two- to four-fold excess of the less valuable alkene **22** - **24** or **28** was combined with epoxyalkene **20** or **21** in $CDCl_3$ solution (to facilitate reaction monitoring by ^1H NMR of aliquots) and the Grela catalyst **30** (2 - 4 mol %), and warmed to 35 °C. After 30 minutes, the reaction mixture was concentrated under vacuum to remove ethylene and solvent, affording the corresponding epoxyalkenes **32** - **33** and **35** - **39** (Figure 5 and Table 1, entries 1 - 2 and 4 - 8). The *cis*-epoxyalkene **34** was prepared using the Grubbs *Z*-catalyst **31** (Table 1, entry 3).[21] When the Grela catalyst was used for cross-metathesis between two chiral non-racemic components, epoxyalkenes **20** or **21** and allylic acetate **28**, the diastereomer ratio of products **35** and **36** was typically higher than expected from statistical analysis (Table 1, entries 4 - 5). This unexpected enhancement of stereoselectivity suggested a mismatch between the minor enantiomer of one component with the major enantiomer of the other chiral alkene.



Grubbs II catalyst (**29**) Grela catalyst (**30**) Grubbs *Z*-catalyst (**31**)

Figure 4. Catalysts for cross-metathesis (Table 1)

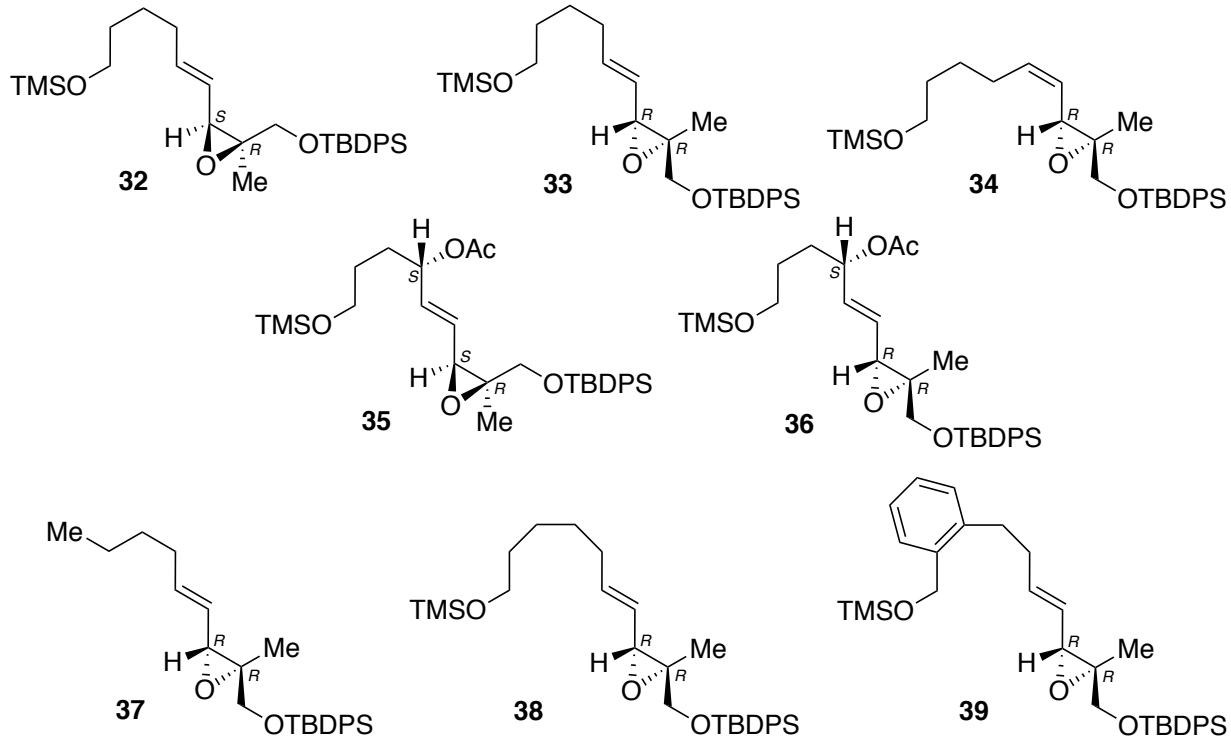


Figure 5. Products arising from cross-metathesis (Table 1)

Table 1. Cross-metathesis for syntheses of substrate precursors **32** - **39**

entry	alkene, equiv (er)	epoxyalkene (er)	catalyst (loading)	product	isolated yield	*trans:cis* (dr)[b]
1	**22**, 4 equiv	**20** (80:20)	**30** (5 mol %)	**32**	[a]	90:10
2	**22**, 3 equiv	**21** (95:5)	**30** (2 mol %)	**33**	[a]	89:11
3	**22**, 3 equiv	**21** (95:5)	**31** (4.4 mol %)	**34**	24%	10:90
4	**28**, 2 equiv (96:4)	**20** (80:20)	**30** (4 mol %)	**35**	61%	>98:2 (86:14)[b]
5	**28**, 2 equiv (96:4)	**21** (95:5)	**30** (4 mol %)	**36**	54%	97:3 (91:9)[b]
6	1-hexene, 8 equiv	**21** (95:5)	**30** (2.5 mol %)	**37**	94%	88:12
7	**23**, 3 equiv	**21** (95:5)	**30** (3.5 mol %)	**38**	45%	90:10
8	**24**, 2 equiv	**21** (95:5)	**30** (3 mol %)	**39**	72%	89:11

[a] The product was not isolated until after the deprotection step (see Table 2). [b] The dr for products **35** and **36** arises from coupling the chiral allylic acetate **28** with the chiral epoxyalkenes **20** or **21**.

Chemoselective deprotections of the cross-metathesis products revealed the hydroxyl groups of epoxyalkene substrates **40** - **48** (Figure 6). We observed that the TMS ethers were removed by methanolysis promoted by either K_2CO_3 (Table 2, entries 1, 2, and 9) or NH_4Cl (entries 3 and 8), affording epoxyalkene substrates **40** - **42** and **47** - **48**. K_2CO_3-promoted methanolysis removed both the trimethylsilyl ether and acetate ester protective groups from compounds **35** and **36**, providing diols **43** and **44** (entries 4 - 5), whereas NH_4Cl-promoted methanolysis exclusively removed the primary trimethylsilyl ethers to furnish the corresponding monoacetates **45** and **46** (entries 6 - 7).

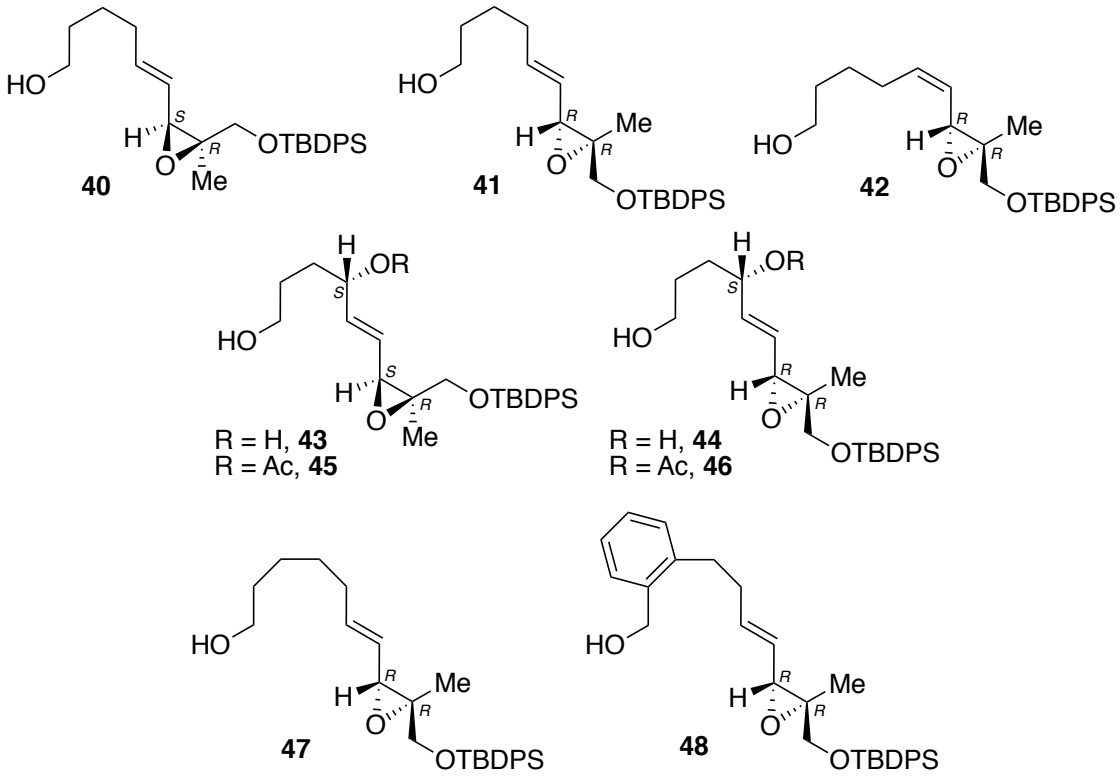


Figure 6. Deprotected epoxyalkene substrates (Table 2)

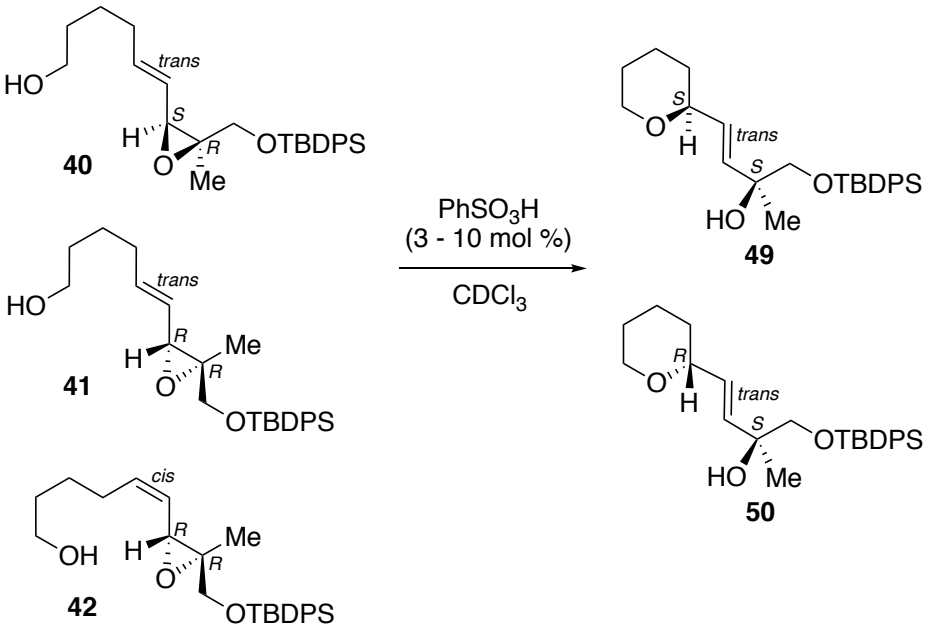
Table 2. Deprotections of hydroxyl groups providing epoxyalkene substrates **40** - **48** (Figure 6)

entry	reactant	product	conditions	isolated yield
1	**32**	**40**	K_2CO_3, MeOH, 1 h	70%[a]
2	**33**	**41**	K_2CO_3, MeOH, 1 h	41%[a]
3	**34**	**42**	NH_4Cl, MeOH, 5 h	83%
4	**35**	**43**	K_2CO_3, MeOH, 3.5 h	53%
5	**36**	**44**	K_2CO_3, MeOH, 3.5 h	55%
6	**35**	**45**	NH_4Cl, MeOH, 3 h	80%
7	**36**	**46**	NH_4Cl, MeOH, 3 h	44%
8	**38**	**47**	NH_4Cl, MeOH, 5 h	88%
9	**39**	**48**	K_2CO_3, MeOH, 1 h	99%

[a] Isolated yield after cross-metathesis (Table 1) and desilylation (2 steps)

Brønsted acid-catalyzed cycloisomerizations: Prior to our first successful palladium-catalyzed cyclizations (vide infra), we serendipitously discovered an analogous process *catalyzed exclusively by Brønsted acids*. In an attempt to deprotect a silyl ether from an epoxyalkene substrate with pyridinium *p*-toluenesulfonate (PPTS) in ethanol,[22] a mixture of compounds was obtained exhibiting the ^{1}H NMR resonances expected for a pyran. Reactions of epoxyalkenes with *p*-toluenesulfonic acid monohydrate were complicated by epoxide ring-opening side reactions with water, but the reaction of (*S,R*)-epoxyalkene substrate **40** *with anhydrous benzenesulfonic acid* in THF produced a mixture of pyranyl alcohols **49** and **50** (Table 3, entry 1). The corresponding reaction with the (*R,R*)-epoxyalkene diastereomer **41** exhibited slight preference for one diastereomer, subsequently characterized as the (*R,S*)-diastereomer **50** (entry 2). Both diastereomers **49** and **50** were exclusively formed as *trans*-alkenes. In $CDCl_3$ solvent, the diastereoselectivities of the $PhSO_3H$-catalyzed process were higher. Thus the epoxyalkene **40** was rapidly converted primarily to the pyranyl alcohol diastereomer **49** (entry 3), and the corresponding transformation with epoxyalkene **41** produced the complementary diastereomer **50** (entry 4), demonstrating a modest level of stereospecificity arising from epoxide stereochemistry. $PhSO_3H$ catalyst loading and reaction conditions were optimized in $CDCl_3$ for the cyclization of an 89:11 mixture favoring the *trans*-alkene of the (*R,R*)-epoxide substrate **41**, giving an 82:18 mixture of diastereomers favoring (*R,S*)-pyranyl alcohol **50** (entry 5). To test for stereospecificity arising from alkene stereochemistry, a 90:10 mixture favoring the *cis*-alkene **42** with (*R,R*)-epoxide stereochemistry identical to substrate **41** underwent cycloisomerization to provide the (*S,S*)-pyranyl alcohol **49** (entry 6). These experiments revealed that the cyclizations in $CDCl_3$ were highly but not completely stereospecific, as in all cases the diastereomer ratios of pyranyl alcohols **49** : **50** were measurably lower than the *trans*:*cis* ratios of epoxyalkene substrates **40** - **42**.[23]

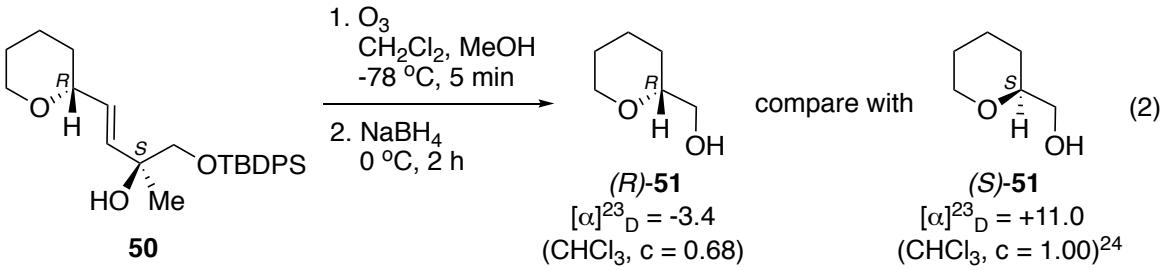
Table 3. Stereoselectivity of $PhSO_3H$-catalyzed cycloisomerizations of epoxyalkenes **40** - **42**



entry	epoxyalkene (*trans*:*cis*)	$PhSO_3H$	solvent	time	dr, **49**:**50**	isolated yield (conversion)
1	**40** (86:14)[a]	10 mol %	THF	4.5 h	52:48	(>90%)
2	**41** (85:15)[a]	10 mol %	THF	4.5 h	36:64	(>90%)
3	**40** (86:14)[a]	10 mol %	$CDCl_3$	5 min	70:30	(>90%)
4	**41** (85:15)[a]	10 mol %	$CDCl_3$	10 min	24:76	(>90%)
5	**41** (89:11)	3 mol %	$CDCl_3$	2.5 h	18:82	87%
6	**42** (10:90)	3 mol %	$CDCl_3$	3.5 h	83:17	90%

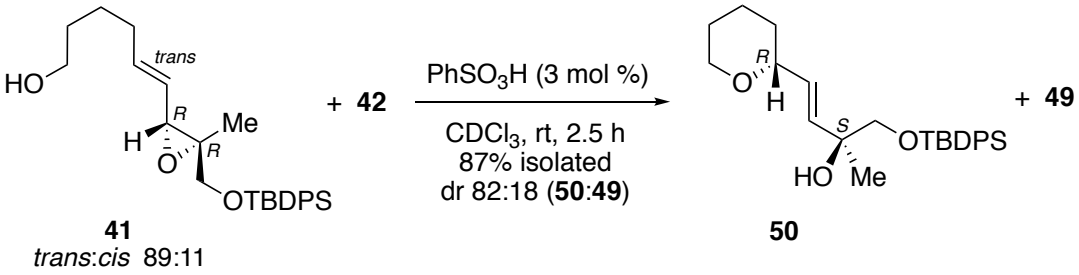
[a] For these experiments, epoxyalkenes **40** and **41** were produced and tested prior to optimizing the *trans*:*cis* stereoselectivity in the cross-metathesis step of substrate synthesis.

The stereochemistry of the pyran chiral center was established by ozonolysis of product **50** (dr 85:15) and reductive workup, affording the known tetrahydropyranmethanol **51** (eq 2). The optical rotation of our synthetic **51** exhibited the opposite sign from the (*R*)-enantiomer of **51** arising from deoxygenation of D-galactose.[24]



50

To gain insights into the mechanism, the $PhSO_3H$-catalyzed cycloisomerizations of substrates **41** and **42** were monitored by ^1H NMR (Figures 7 - 10). We calibrated integrals with the TBDPS *tert*-butyl group, and acquired data at five-minute intervals. These experiments showed nearly linear formation of the pyran products over time, along with a linear decrease of the concentration of the epoxyalkene substrates. This work also revealed that the *trans*-alkene substrate **41** was considerably more reactive than the *cis*- substrate **42**. For instance, with an 89:11 mixture of **41**:**42** favoring the *trans*-alkene substrate **41** (Figures 7, 8), the concentration of the minor *cis*-alkene **42** remained relatively constant until all of the *trans*-alkene **41** had been consumed. Conversely, with a 90:10 mixture favoring the *cis*-alkene substrate **42** (Figures 9, 10), the minor *trans*-alkene isomer **41** was rapidly consumed in the first hour of the reaction.



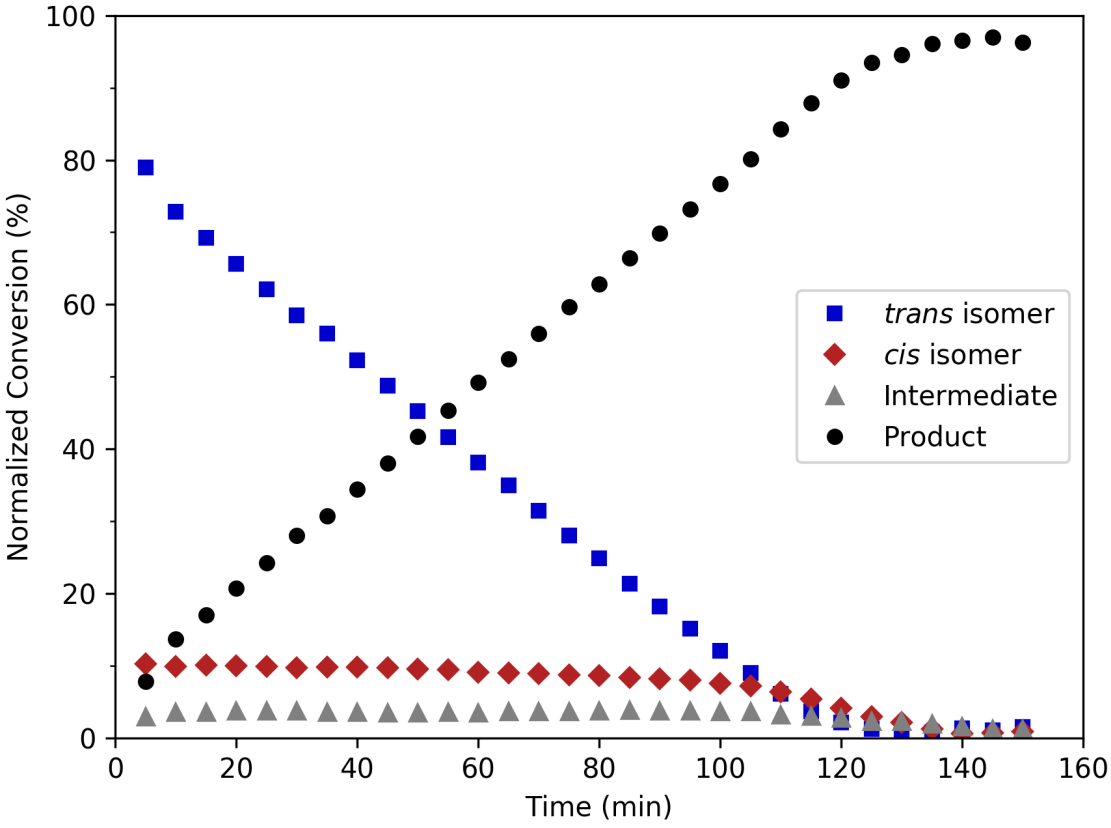


Figure 7. Normalized NMR conversion of species in $PhSO_3H$-catalyzed cycloisomerization of epoxyalkene mixture favoring *trans*-alkene **41**

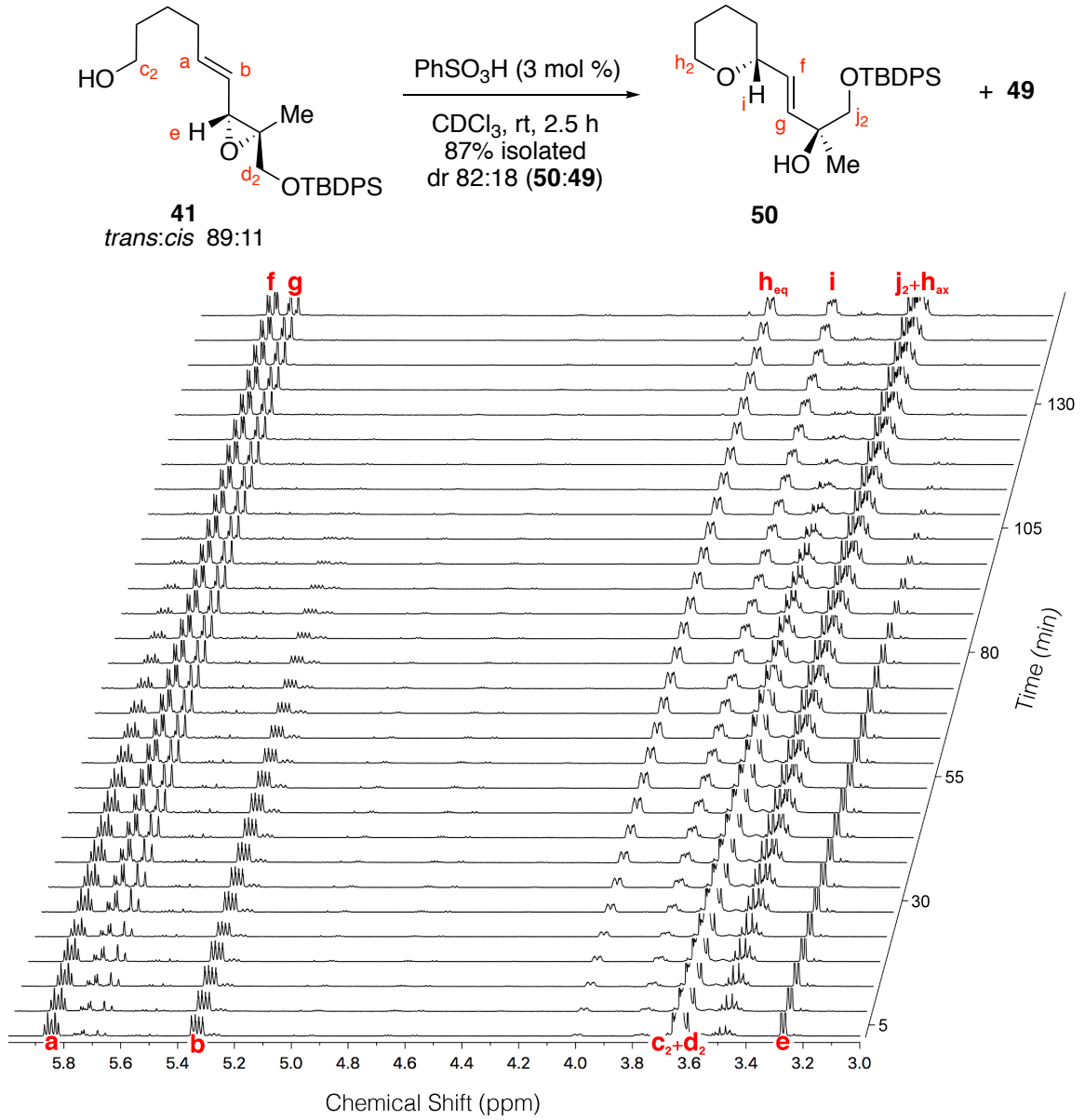
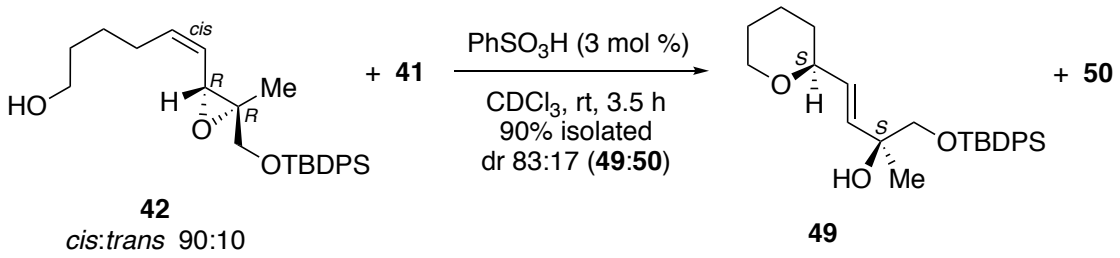


Figure 8. NMR time course, showing disappearance of *trans*-alkene **41** and appearance of pyranyl alcohol **50**, at five minute intervals



42
cis:*trans* 90:10

49

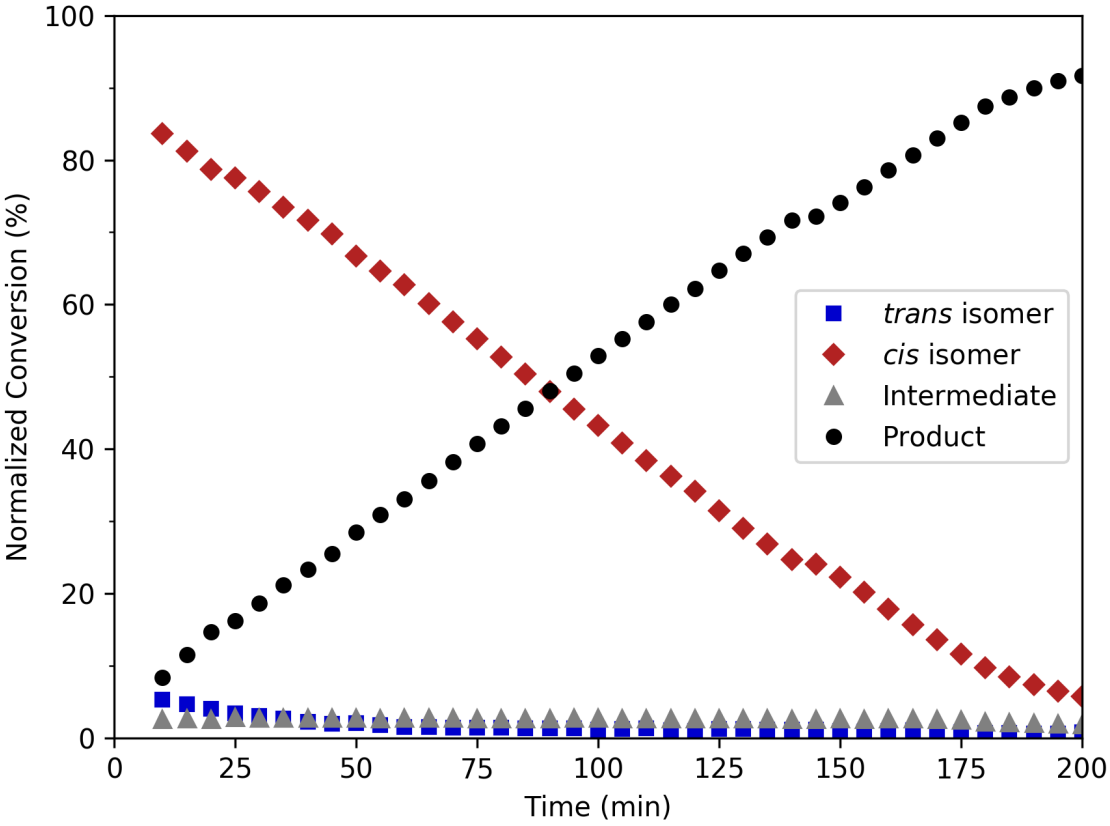
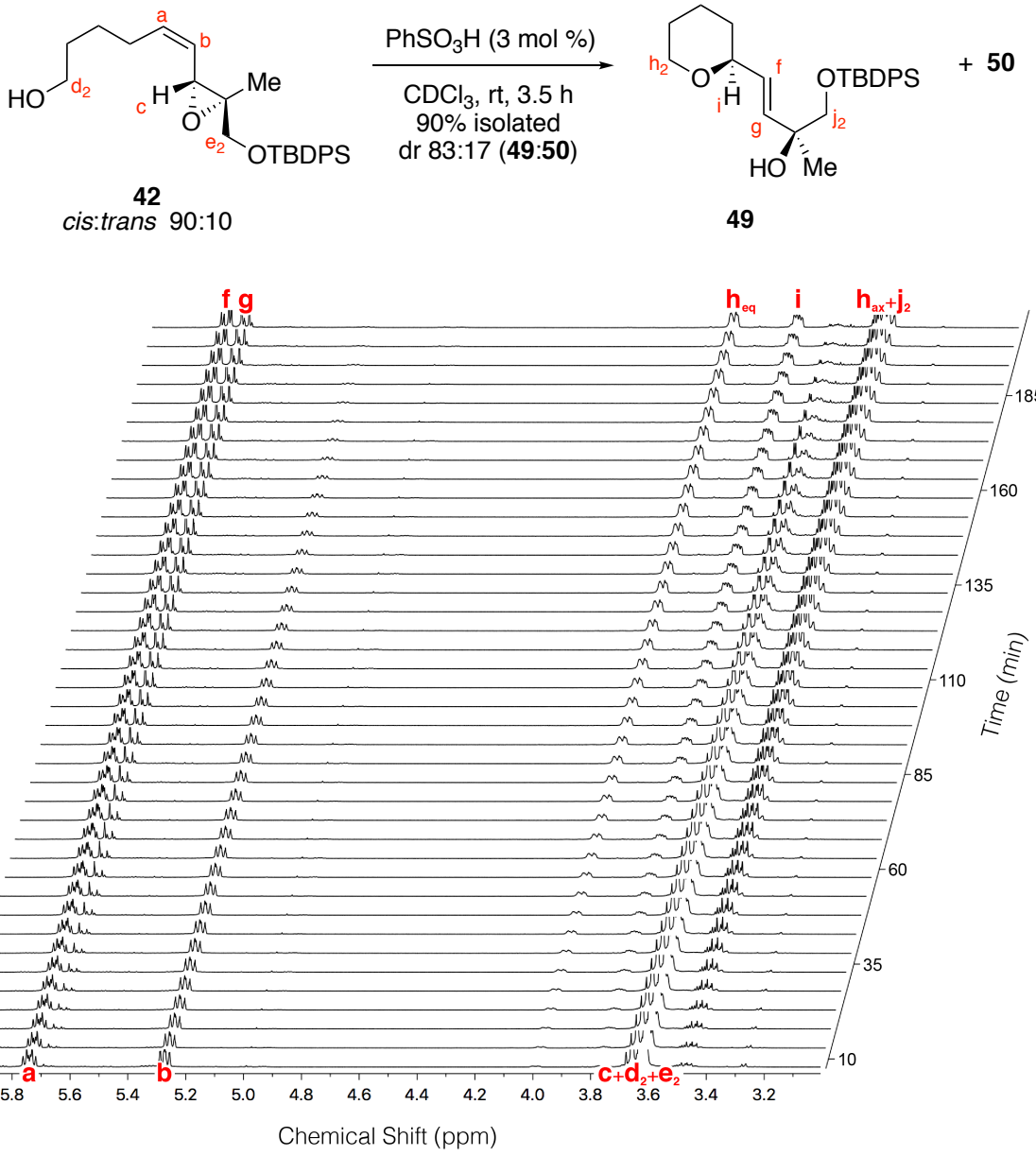


Figure 9. Normalized NMR conversion of species in cyclization of substrate mixture favoring *cis*-alkene **42**

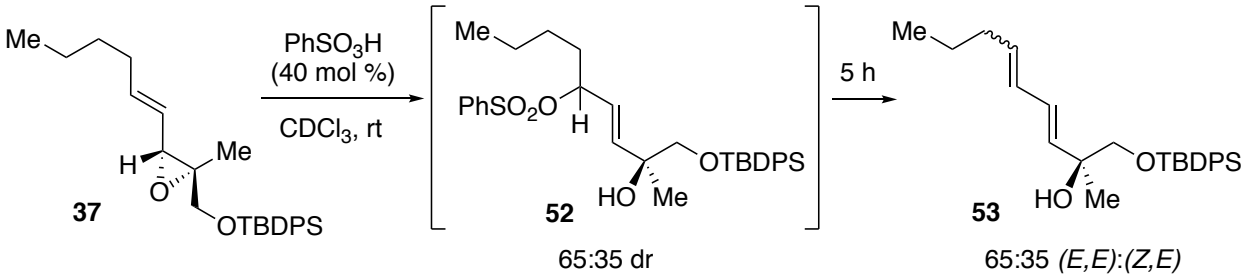


42
cis:*trans* 90:10

49

Figure 10. NMR time course, showing disappearance of *cis*-alkene **42** and appearance of pyranyl alcohol **49**, at five minute intervals

In both studies (Figures 7, 9), we also observed an intermediate in the ^{1}H NMR spectra with a normalized concentration consistent with the acid catalyst loading (ca. 3%), suggesting the possibility of an allylic sulfonate intermediate. To gain better insight into the nature of this intermediate, the $PhSO_3H$-promoted reaction of epoxyalkene **37** was studied, as this compound was incapable of cyclization. With 40 mol % of benzenesulfonic acid, the epoxyalkene **37** gave a mixture of two diastereomers of a metastable product **52** in a relatively high concentration (Figure 11). This compound could not be isolated, but the chemical shift of the methine hydrogen at 4.97 ppm was similar to the literature value for the methylene hydrogens of allyl tosylate (4.5 ppm).[25] Allylic benzenesulfonate **52** was accompanied by formation of the diene **53**, which may have arisen from elimination of intermediate **52**. NOE correlations were observed in intermediate **52** between H_a on the benzensulfonate and H_b, H_c and H_d, providing strong evidence for our assignment of the allylic benzenesulfonate intermediate.



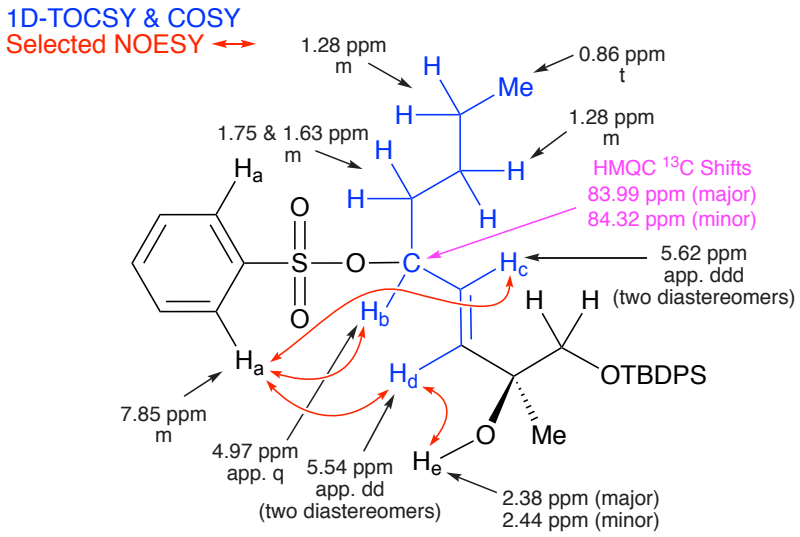
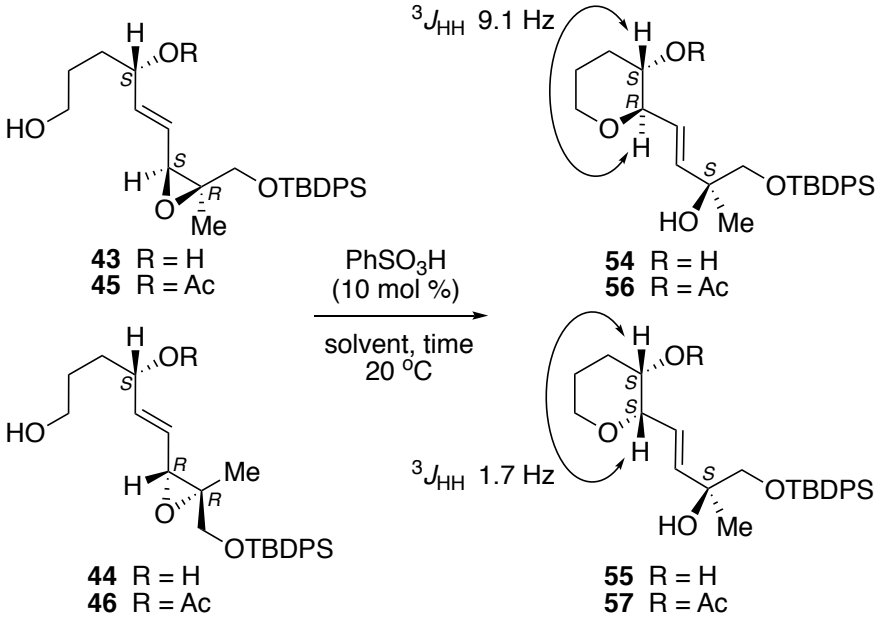


Figure 11. Reaction of epoxyalkene **37** with benzenesulfonic acid, and NMR evidence for allylic benzenesulfonate intermediate **52**

From $PhSO_3H$-catalyzed cycloisomerizations of the more complex substrates **43** - **44**, we established that cyclizations were slower in THF than in $CDCl_3$, as we had observed with epoxyalkenes **40** and **41**. Moreover, cyclizations of either epoxyalkene diastereomer **43** or **44** in THF favored the same pyranyl diol diastereomer **55** (Table 4, entries 1, 2). In contrast, complementary stereoselectivity was exhibited for $PhSO_3H$-catalyzed cyclizations in $CDCl_3$, with epoxyalkene **43** leading predominantly to pyranyl diol **54** (entry 3), and the diastereomeric epoxyalkene **44** giving higher stereoselectivity for pyranyl diol **55** (entry 4). As the pyranyl diols **54** and **55** were unstable upon prolonged exposure to the reaction conditions,[26] the cyclizations of the corresponding allylic acetates **45** and **46** were also studied with $PhSO_3H$ catalysis,

producing the respective pyrans **56** and **57** (entries 5, 6). The stereochemistry of each pyran was assigned from the coupling constants between the hydrogens at the adjacent chiral centers, with the *trans*-configuration of (*S,R*)-pyran **56** consistent with a larger coupling constant for the axial hydrogens at the adjacent chiral centers than observed for the (*S,S*)-diastereomer **57**.

Table 4. Brønsted acid-catalyzed cycloisomerizations of epoxyalkenes **43** - **46**



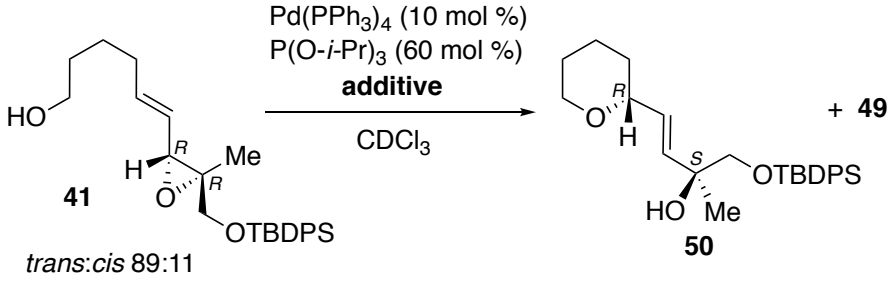
entry	epoxyalkene (dr)	solvent	time	products (dr)	conversion
1	**43** (86:14)	THF	22 h	**54** + **55** (38:62)	(>90%)
2	**44** (89:11)	THF	22 h	**54** + **55** (37:63)	(>90%)
3	**43** (86:14)	$CDCl_3$	2 h	**54** + **55** (63:37)	(ca. 50%)
4	**44** (89:11)	$CDCl_3$	2 h	**54** + **55** (15:85)	(>90%)
5	**45** (83:17)[a]	$CDCl_3$	2.5 h	**56** + **57** (74:26)	(>90%)
6	**46** (95:5)	$CDCl_3$	2.5 h	**56** + **57** (17:83)	(>90%)

[a] In this experiment, substrate **45** was produced and tested prior to optimizing its synthesis.

Overall, these results indicate that the $PhSO_3H$-catalyzed cycloisomerization involves two steps: stereoselective addition of benzenesulfonic acid to the epoxyalkene in an S_N' fashion, followed by intramolecular substitution of the primary alcohol, displacing the allylic benzenesulfonate with inversion of configuration. This mechanism is consistent with the complementary sense of stereoinduction arising from substrates **40** - **46** in forming the corresponding pyran products **49 - 50** and **54** - **57** (Tables 3, 4). However, the Brønsted acid-catalyzed process was limited with regard to yields and diastereoselectivities, and could not be extended to preparing seven-membered ring products from substrate **47**. With the mechanistic insights on the role of Brønsted acids on epoxide opening, we returned to the study of palladium catalysis for this transformation.

Palladium-catalyzed cycloisomerizations: With an aim to improving on the Brønsted acid-catalyzed process, we investigated the cyclization of substrate **41** with $Pd(PPh_3)_4$ and P(O-*i*-Pr)$_3$,[27] *in the presence of various Lewis and Brønsted acids* (Table 5). This work revealed that acidic additives were essential to the success of palladium-catalyzed cycloisomerizations. Diphenylphosphinic acid ($Ph_2P(O)OH$) was the best additive for these Pd-catalyzed cyclizations, rapidly furnishing the pyran product **50** with good diastereoselectivity (Table 5, entry 9).[28] This reaction went to completion with identical diastereoselectivity in $CDCl_3$, CH_2Cl_2 and THF, although the reaction progress was slightly slower in THF.

Table 5. An acidic additive is required for Pd-catalyzed cycloisomerizations of epoxyalkene **41**

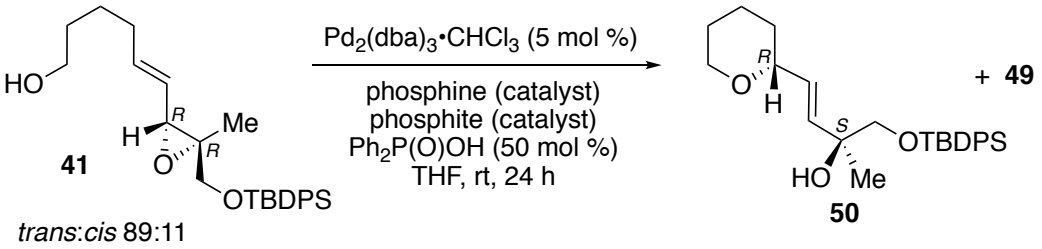


entry	additive (equiv)	time	conversion	dr (**50**:**49**)
1	(none)	3 h	(no reaction)	-
2	$Zn(OTf)_2$ (1.1)	3 h	80%[a]	64:36
3	$Zn(OTf)_2$ (1.1)	6 d	52%[b]	63:37
4	$Cu(OTf)\bullet(MeCN)_4$ (1.3)	3 h	86%[a]	58:42
5	$Cu(OTf)\bullet(MeCN)_4$ (1.3)	6 d	50%[b]	ND[c]
6	Ti(O-*i*-Pr)$_4$ (0.9)	6 d	38%[a]	77:23
7	Ti(O-*i*-Pr)$_4$ (0.9)	15 d	>95%	80:20
8	ClTi(O-*i*-Pr)$_3$ (0.9)	17 h	>95%	80:20
9	**$Ph_2P(O)OH$ (0.9)**	**1 h**	**>95%**	**83:17**
10	AcOH (82)[d]	24 h	76%[e]	85:15

[a] The remainder was epoxyalkene **41**. [b] Epoxyalkene **41** was completely consumed; the remaining material was identified as a spiroketal derived from the pyran products. [c] The diastereomer ratio could not be determined because of line broadening induced by paramagnetic copper species. [d] In THF solvent. [e] The remaining 24% corresponded to addition of acetic acid instead of cycloisomerization.

In optimizing the ligands for the Pd-catalyzed process, we determined that $P(O\text{-}i\text{-}Pr)_3$ was required for the cycloisomerization of **41** to **50** (Table 6, entry 3). The best yield and highest diastereoselectivity were obtained with both $P(O\text{-}i\text{-}Pr)_3$ and PPh_3 (entry 4).

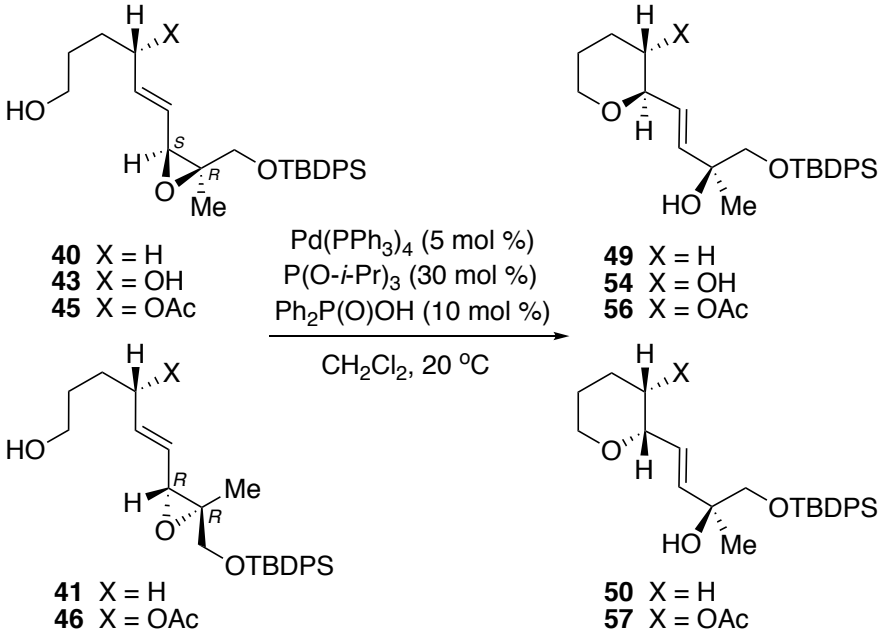
Table 6. Ligand investigations of Pd-catalyzed cycloisomerizations of epoxyalkene **41**



entry	phosphine	phosphite	conversion	dr (**50**:**49**)
1	(none)	(none)	(no reaction)	-
2	PPh_3 (50 mol %)	(none)	trace	-
3	(none)	$P(O\text{-}i\text{-}Pr)_3$ (80 mol %)	92%	83:17
4	**PPh_3 (50 mol %)**	**$P(O\text{-}i\text{-}Pr)_3$ (40 mol %)**	**100%**	**85:15**
5	PCy_3 (50 mol %)	$P(O\text{-}i\text{-}Pr)_3$ (40 mol %)	78%	85:15
6	dppp (25 mol %	$P(O\text{-}i\text{-}Pr)_3$ (40 mol %)	44%	81:19

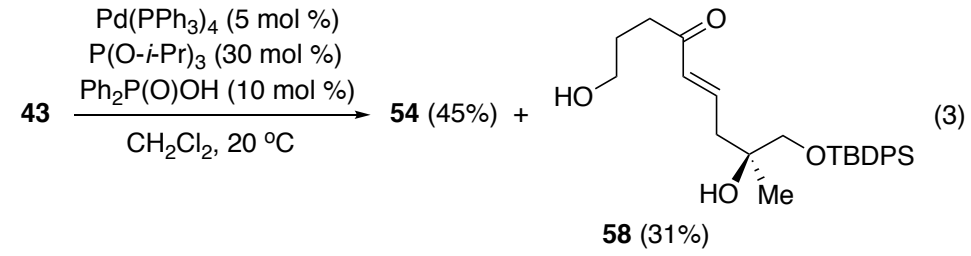
This transformation was further optimized in CH_2Cl_2 solvent and generalized with several substrates, using $Pd(PPh_3)_4$ as the source of both palladium and the triphenylphosphine ligand, and decreasing the loading of the phosphite ligand and the Brønsted acid catalyst (Table 7). Under identical conditions, the epoxyalkene substrates **40** and **41** produced the corresponding pyranyl alcohol diastereomers **49** and **50** (entries 1, 2). The allylic alcohol substrate **43** gave modest isolated yield of the pyranyl diol **54** under the Pd-catalyzed conditions (entry 3), accompanied by substantial formation of an acyclic enone byproduct **58** (eq 3).[29] We hypothesized that the enone **58** may have arisen from hydride migration from the secondary carbinol of **43**. This side reaction was effectively suppressed with the corresponding acetate ester **45** and its diastereomer **46**, which were converted into the corresponding pyranyl alcohol diastereomers **56** and **57**, respectively (entries 4, 5). The chemoselectivity of these cyclizations was notable, as oxidative addition of the epoxyalkene with Pd(0) was favored over the reaction of the allylic acetates **56** and **57**. In all cases, the Pd-catalyzed method proceeded with the same sense of stereoinduction as observed with the $PhSO_3H$-catalyzed process, but with uniformly higher diastereoselectivities, consistent with a greater degree of stereospecificity linking chirality and mechanism.

Table 7. Optimized conditions for Pd-catalyzed cycloisomerizations of epoxyalkenes



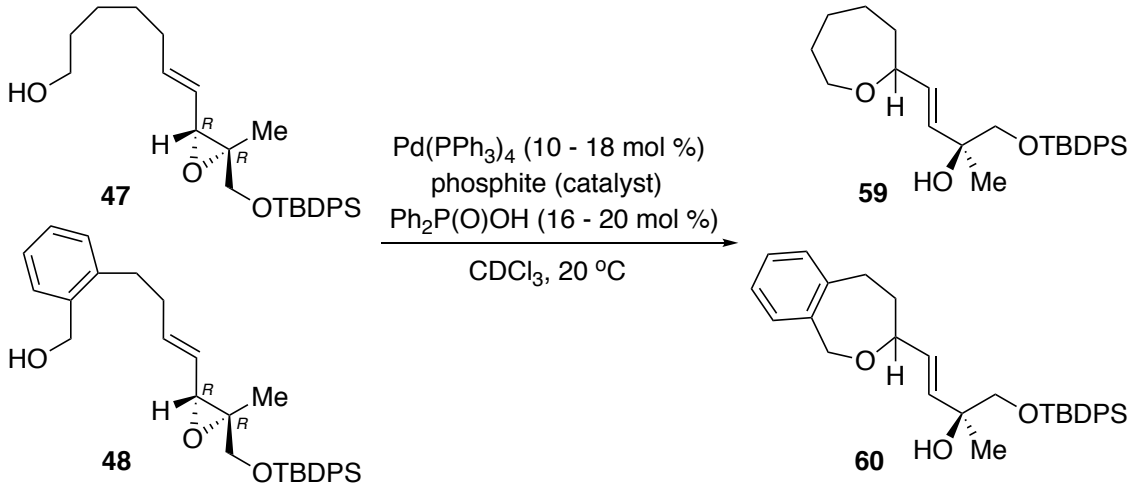
	epoxyalkene substrate			pyran product		
entry		*trans*:*cis*	dr[a]		isolated yield	dr
1	**40**	90:10	n/a	**49**	84%	88:12
2	**41**	89:11	n/a	**50**	88%	85:15
3	**43**	>98:2	86:14	**54**	45%[b]	94:6
4	**45**	95:5	85:15	**56**	61%	81:19
5	**46**	>95:5	93:7	**57**	62%	92:8

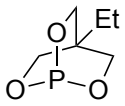
[a] The diastereomer ratios refer to the ratio of the secondary allylic alcohol or acetate (X = OH or OAc) to both stereoisomers of the epoxide. [b] Acyclic enone **58** was also isolated in 31% yield (eq 3).



Initial efforts to apply Pd-catalysis to the cycloisomerization of epoxyalkene substrate **47** gave only partial conversion and low yield of seven-membered ring oxepane **59**, even with higher catalytic loading and prolonged reaction time (Table 8, entry 1). However, the conformationally restricted substrate **48** provided more promising results, giving high conversion within two hours to provide benzooxepane **60** (entry 2). We subsequently observed better results in the cycloisomerization of epoxyalkene **47** using trimethylolpropane phosphite **61** (EtCage),[30] a ligand known to enhance the rates of other Pd-catalyzed processes, achieving greater than 90% conversion to the oxepane **59** (entry 3). An additional benefit of the EtCage ligand was that the oxepane product **59** was produced with diastereoselectivity very close to the *trans*:*cis* ratio of epoxyalkene **47**.

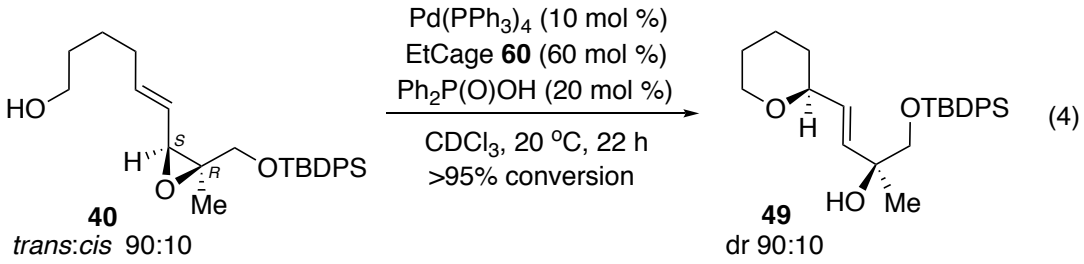
Table 8. Syntheses of oxepanes by palladium-catalyzed cycloisomerizations



entry	epoxyalkene	*trans*:*cis*	phosphite ligand	oxepane product [a]	conversion (isolated yield)	dr
1	**47**	88:12	P(O-*i*-Pr)$_3$ (120 mol %)	**59**	ca. 58% conversion (21% yield)[b]	ND
2	**48**	89:11	P(O-*i*-Pr)$_3$ (120 mol %)	**60**	>90% conversion (42% yield)	87:13
3	**47**	83:17	 (60 mol %) **61** (EtCage)	**59**	>90% conversion (25% yield)[c]	82:18

[a] The stereochemical assignments for the major diastereomers of **59** and **60** were not determined. [b] In addition to ca. 42% of **47** still present, byproducts included an acyclic diene (ca. 20%) and incorporation of diphenylphosphonite (ca. 17%). [c] The low isolated yield may be due to the small scale of this experiment.

In the conversion of epoxyalkene **40** to pyranyl alcohol **49**, the reaction rate was considerably *slower* with EtCage ligand **61** relative to P(O-*i*-Pr)$_3$ (eq 4), but now the diastereoselectivity of **49** matched the *trans*:*cis* ratio of epoxyalkene reactant **40**.



Based on these results, we propose a mechanism for the dual catalytic process with palladium and Brønsted acid, depicted for the conversion of allylic acetate epoxyalkene **45** to pyran **56** (Figure 12). The catalytic cycle begins with coordination of Pd(0) to the alkene of the epoxyalkene **45** along with protonation of the epoxide, to give **62**. The protonated epoxide is now activated for oxidative addition of Pd, furnishing π-allyl complex **63**. Intramolecular addition of the alcohol to the π-allylpalladium intermediate and regeneration of diphenylphosphinic acid generates the product as the π-complex **64**. Dissociation of palladium from **64** closes the catalytic cycle and releases the pyran product **56**.

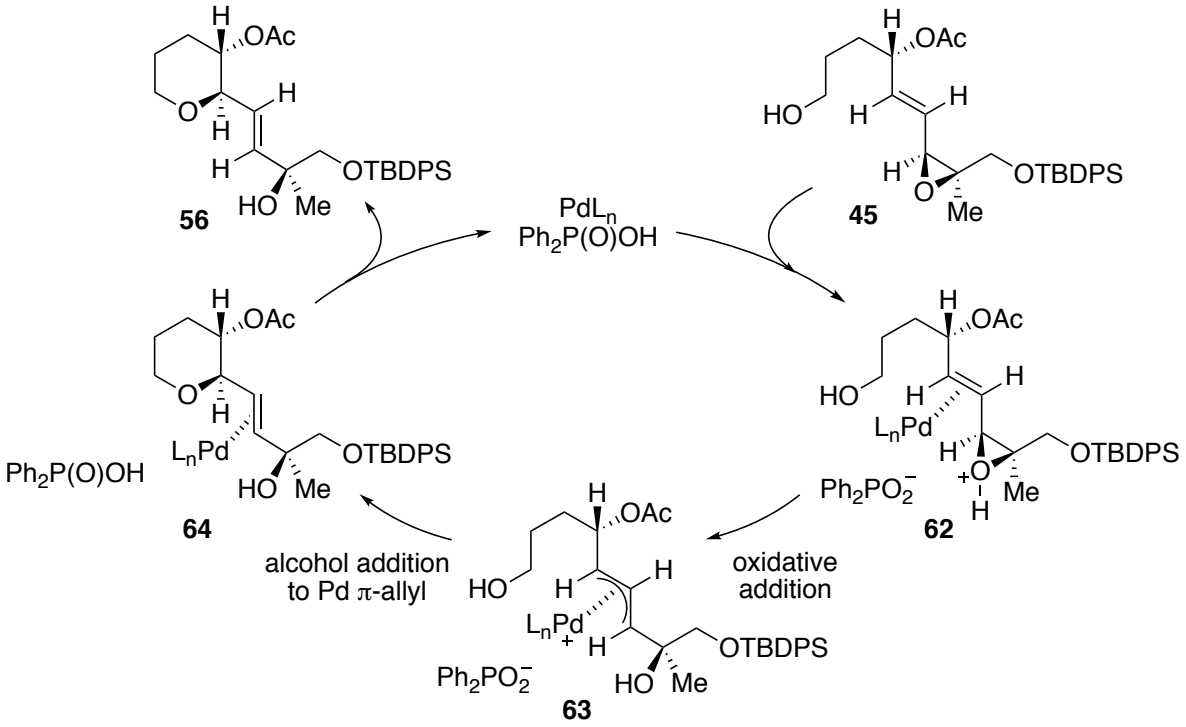


Figure 12. Working hypothesis for catalytic cycle

CONCLUSION

In summary, we have developed palladium-catalyzed conditions for the stereoselective formation of either pyran diastereomer, corresponding to the choice of epoxyalkene diastereomer. The addition of $Ph_2P(O)OH$ as a Brønsted acid co-catalyst is essential for these cyclizations. Brønsted acid-catalyzed cycloisomerizations give the same sense of stereospecificity as the Pd-catalyzed transformations, but with lower stereoselectivity and a greater propensity for acid-catalyzed product decomposition pathways. Future activities along these lines will include applications to the stereoselective synthesis of fused polycyclic ethers.[31,32]

EXPERIMENTAL SECTION

General experimental: Proton and carbon NMR spectra were recorded on MERCURY 300 (300 MHz), INOVA-400 (400 MHz), VNMRS 400 (400 MHz), INOVA-500 (500 MHz), INOVA-600 (600 MHz), Unity-600 (600 MHz) or a BRUKER 600 (600 MHz) instrument equipped with cryogen probe. NMR spectra were recorded in solutions of deuterated chloroform ($CDCl_3$) with the residual chloroform (7.27 ppm for ^1H NMR and 77.23 ppm for ^{13}C NMR) taken as the internal standard, deuterated methanol (CD_3OD) with residual methanol (3.31 ppm for ^1H-NMR and 49.3 ppm for ^{13}C-NMR) taken as the internal standard, or deuterated benzene with residual benzene (7.16 ppm for ^1H NMR and 128.23 ppm for ^{13}C NMR) taken as the internal standard, and were reported in parts per million (ppm). With the exception of the diastereomeric ratios of the epoxyalkene cross metathesis products, all drs, ers (of Mosher esters) and *trans:cis* ratios were determined by NMR integration of isolated peaks with an uncertainty of ±2%. Abbreviations for signal coupling are as follows: s, singlet; d, doublet; t, triplet; q, quartet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; m, multiplet. IR spectra were collected on a Nicolet iS10 from Thermo Scientific and reported in units of cm^{-1}. Mass spectra (high resolution ESI and APCI) were recorded on a Thermo LTQ (linear quadrupole ion trap) FTMS (Fourier transform mass spectrometer) based on ion cyclotron resonance mass spectrometry (ICR-MS). Optical rotations were measured using a Perkin-Elmer 341 polarimeter (concentration in g/100mL). Thin layer chromatography (TLC) was performed on pre-coated glass-backed plates purchased from Whatman (silica gel 60F254; 0.25mm thickness). Preparative TLC was performed on pre-coated glass-backed plates purchased from Analtech (20 x 20 cm, Silica gel GF UV254, 1.0 mm thickness). Flash column chromatography was carried out with silica gel 60 (230-400 mesh ASTM) from Silicycle. All reactions were carried out with anhydrous solvents in oven dried or flame dried and argon-charged glassware unless otherwise specified. All anhydrous solvents were dried with 4Å molecular sieves purchased from Sigma-Aldrich and tested for trace water content with Coulometric KF titrator from Denver instruments. All solvents used in extraction procedures and chromatography were used as received from commercial suppliers without prior purification. All metathesis catalysts were purchased from Sigma Aldrich, except for the nitro-Grela catalyst, which was purchased from Strem Chemical.

Mosher (MTPA) ester derivatives were prepared in the following fashion:[33] the secondary alcohol (2 - 10 mg) was dissolved in dry $CDCl_3$ (1.2 mL). From a freshly opened ampule of d_5-pyridine, 12 drops was added to this solution. The mixture was then partitioned between two new NMR tubes sparged with Ar. To each tube was added one drop (as dispensed from a short Pasteur pipette using thumb pressure) of one enantiomer of the MTPA acid chloride. The NMR tubes were inverted several times to mix and then allowed to stand for 24 h before NMR analysis. For primary alcohols, the reaction was much faster. Substrates containing epoxides were prone to degradation upon standing, thus were analyzed within an hour of adding the MTPA acid chloride.

*Preparation of (Z)-3-iodo-2-methylprop-2-en-1-ol **14***: CuI (2.77 g, 14.5 mmol) was suspended in THF (150 mL) at 0,°C and MeMgBr (100 mL, 300 mmol, 3 M in Et_2O) was added by cannula. Propargyl alcohol (**13**, 9.0 mL, 8.55 g, 152.5 mmol) was added slowly to this solution (Caution! vigorous gas evolution). The mixture was stirred at 0 °C for 45 min, whereupon a solution of I_2 (38.3 g, 150.9 mmol) in Et_2O (250 mL) was added slowly. The mixture was removed from the cooling bath, stirred for 30 min and poured directly into a separatory funnel charged with sat. NH_4Cl (150 mL) and brine (150 mL). Solid $Na_2S_2O_3$ was added in portions to remove unreacted iodine from the organic layer (turning it from brown to yellow). The layers were separated and the blue aqueous layer (likely due to formation of copper ammine) was extracted with Et_2O (3 x 250 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a yellow oil (15.95 g). Crude NMR showed the oil to be 93.5% (*Z*)-3-iodo-2-methylprop-2-en-1-ol **14** by weight (14.91 g, 75.3 mmol, 50% yield), the remaining mass being 2-methyl-2-propen-1-ol. The oil of this experiment was carried on directly to the next step, but may be purified *via* short path distillation (bp 72 °C, 7 torr) if desired. Spectral data matched that reported in the literature.[8]

*Preparation of (Z)-2-methyl-2,4-pentadien-1-ol **15***: A solution of vinyl iodide **14** (15.95 g, 93.5% by weight, 75.3 mmol) in PhMe (250 mL) was degassed with argon for 20 minutes and cooled to 0. °C. $Pd(PPh_3)_4$ (1.00 g, 0.86 mmol) was added, and the solution aged for 20 minutes, whereupon a solution of vinylmagnesium bromide (200 mL, 200 mmol, 1 M in THF) was added slowly (Caution! Vigorous gas evolution) *via* addition funnel over 10 minutes. The reaction mixture was allowed to warm to room temperature overnight, and quenched with saturated NH_4Cl (200 mL). The solution was further diluted with water (200 mL), the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* (the water bath temperature was kept between 10 and 20 °C) to give an orange oil with some red solids. The oil was filtered though a small pad of cotton with Et_2O and distilled under reduced pressure to give (*Z*)-2-methyl-2,4-pentadien-1-ol **15** as a clear liquid (3.35 g, 34.1 mmol, 45% yield, bp 49–51 °C at 7 torr). Spectral data matched that reported in the literature.[10]

*Preparation of pent-4-en-2-yn-1-ol **16***: To a 1 M solution of vinyl bromide (84 mL, 84 mmol) in THF was added CuI (728 mg, 3.8 mmol), $PdCl_2(PPh_3)_2$ (247 mg, 0.35 mmol) and *i*-Pr_2NH (25 mL, 178 mmol). The mixture was cooled to 0 °C, and propargyl alcohol (**13**, 4.8 mL, 83 mmol) was added dropwise over 5 minutes, whereupon the cooling bath was removed. After aging for 20 h at rt, the reaction mixture was poured into a mixture of saturated aqueous NH_4Cl (100 mL) and Et_2O (50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (3 x 50 mL; for the last extraction, the aqueous layer was diluted with 20 mL water). The combined organics were dried over $MgSO_4$ and concentrated *in vacuo* in a fume hood to give pent-4-en-2-yn-1-ol **16** as a dark red oil (5.55 g, 81% yield). Spectral data matched that reported in the literature.[11b]

*Preparation of (E)-2-methyl-2,4-pentadien-1-ol **17***: To a 0 °C suspension of CuI (1.68 g, 8.8 mmol) in THF (20 mL) was added MeMgBr (3 M in Et_2O, 70 mL, 210 mmol). To the yellow suspension was added dropwise a solution of enynol **16** (5.55 g, 67.6 mmol) in THF (20 mL) over 10 minutes (Caution! vigorous CH_4 evolution). The reaction mixture was allowed to warm to rt over 20 h, and then was quenched slowly at 0 °C *via* addition of a 1:1 mixture of water:saturated NH_4Cl (100 mL). The mixture was further diluted with water (200 mL) and extracted with Et_2O (3 x 100 mL). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* (the water bath temp was kept < 20 °C) to afford (*E*)-2-methyl-2,4-pentadien-1-ol **17** as a red-orange oil (6.18 g, 93% yield). Spectral data matched that reported in the literature.[13]

*Preparation of (S,R)-epoxyalkenyl alcohol **18***: To a suspension of ground activated 3Å molecular sieves (1.86 g) in CH_2Cl_2 (150 mL) at -20 °C was added titanium isopropoxide (0.50 mL, 1.7 mmol) and D-(-)-diisopropyl tartrate (0.55 mL, 2.6 mmol). *Tert*-butyl hydroperoxide (5.5 M in decane, 13.0 mL, 71.5 mmol) was then added to this mixture over 5 min, and the mixture was aged for 30 min. After cooling to -35 °C, a solution of dienyl alcohol **15** (3.35 g, 34 mmol) in CH_2Cl_2 (30 mL) was added slowly. The reaction mixture was stirred at -35 ˚C for 24 h and then warmed to -20 °C, whereupon it was quenched via addition of a 10% NaOH solution in saturated NaCl (2.7 mL). After adding Et_2O (20 mL), the mixture was allowed to warm to 10 ˚C over 2 h, whereupon $MgSO_4$ (2.7 g) and Celite (380 mg) were added, and the mixture stirred for 10 min before filtering through a pad of Celite with Et_2O (~500 mL). The eluant was concentrated *in vacuo,* and the resulting oil was purified by column chromatography eluting with 30/70 EtOAc/Hexanes to give (*S,R*)-epoxyalkenyl alcohol **18** as a clear liquid (3.12 g, 80% yield, 80:20 er by analysis of the corresponding Mosher esters). $[\alpha]_D^{20}$ = +7.0 (CH_2Cl_2, *c* = 0.91); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 5.85 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.50 (ddd, *J* = 17.2, 1.4, 0.9 Hz, 1H), 5.38 (ddd, *J* = 10.5, 1.4, 0.8 Hz, 1H), 3.69 (d, *J* = 6.1 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 1.60 (t, *J* = 5.2 Hz, 1H), 1.45 (s, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 132.5, 121.1, 64.64, 64.56, 64.0, 20.02, 19.97; **IR** (neat) 3418, 2974, 2935, 1740, 1640, 1448, 1377, 1044, 1027 cm^{-1}; **HRMS** (NSI) calculated for $C_6H_{10}O_2Na^+$ $[M+Na]^+$ 137.0573, found 137.0572.

*Preparation of (R,R)-epoxyalkenyl alcohol **19***: To a cooled (-20 °C) suspension of powdered 4Å molecular sieves (3.27 g) in CH_2Cl_2 (200 mL) was added Ti(O*i*-Pr)$_4$ (0.93 mL, 3.1 mmol) and D-(-)-diethyl tartrate (0.68 mL, 3.9 mmol). *t*-BuOOH (5.5 M in decane, 23 mL, 127 mmol) was added dropwise over the course of 5 min. After aging for 45 min at -20 °C, a solution of (*E*)-2-methyl-2,4-pentadien-1-ol **17** (6.18 g, 63 mmol) in CH_2Cl_2 (15 mL) was added portionwise over 15 min. After 2 h at -20 °C, the reaction mixture was quenched via addition of a 10% NaOH solution in saturated NaCl (8 mL). After allowing the mixture to warm to 0 ˚C over 30 min, Et_2O (40 mL) was added followed by $MgSO_4$ (5.5 g) and Celite (0.76 g), and the mixture allowed to warm to 10 °C over 30 min. The solution was filtered through a pad of Celite, and concentration of the crude gave a yellow oil whose NMR showed it to be approximately 2:1 epoxide:diene. The crude oil was purified via flash column chromatography to give (*R,R*)-epoxyalkenyl alcohol **19** as a colorless oil (2.97 g, 41% yield, 54% brsm, er > 95:5 by analysis of the corresponding Mosher esters). Some of the starting diene **17** (1.37 g, 22%) was also recovered. $[\alpha]_D^{20}$ = +9.4 (CH_2Cl_2, *c* = 0.60); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 5.77 (ddd, *J* = 17.2, 10.5, 7.3 Hz, 1H), 5.50 (ddd, *J* = 17.2, 1.5, 0.8 Hz, 1H), 5.40 (ddd, *J* = 10.5, 1.5, 0.8 Hz, 1H), 3.74 (dd, *J* = 12.4, 4.3 Hz, 1H), 3.65 (dd, *J* = 12.4, 8.9 Hz, 1H), 3.57 (d, *J* = 7.3 Hz, 1H), 1.83 (dd, *J* = 8.9, 4.3 Hz, 1H), 1.30 (s, 3H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 132.6, 121.2, 64.9, 62.9, 60.2, 14.4; **IR** (neat) 3408, 2932, 1638, 1451, 1384, 1067, 986, 924, 871, 805, 696, 649 cm^{-1}; **HRMS** (NSI) calculated for $C_6H_{11}O_2$ $[M+H]^+$ 115.0754, found 115.0753.

*Preparation of (S,R)-epoxyalkenyl TBDPS ether **20***: Epoxy alcohol **18** (2.31 g, 20.3 mmol) and imidazole (1.51 g, 22.1 mmol) were dissolved in dry DMF (20 mL) and cooled to 0 °C, and TBDPSCl (5.20 mL, 5.51 g, 20.3 mmol) was added. The reaction mixture was allowed to warm to rt overnight, diluted with water (100 mL) and extracted with Et_2O (5 x 50 mL). The combined organic layers were back-extracted with water (5 x 50 mL), washed with brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude oil was subjected to column chromatography eluting with 5/95 Et_2O/Hexanes to give silyl ether **20** as a white, amorphous, waxy solid (5.47 g, 15.5 mmol, 76% yield). $[\alpha]_D^{20}$ = +10.7 (CH_2Cl_2, *c* = 0.65); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.47-7.37 (m, 6H), 5.60 (ddd, *J* = 17.2, 10.4, 6.8 Hz, 1H), 5.37 (ddd, *J* = 17.1, 1.5, 0.8 Hz, 1H), 5.22 (ddd, *J* = 10.5, 1.5, 0.7 Hz, 1H), 3.68 (dd, *J* = 17.2, 10.9 Hz, 2H), 3.29 (d, *J* = 6.9 Hz, 1H), 1.51 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 135.85, 135.80,

133.5, 133.3, 132.6, 129.9, 127.9, 120.2, 65.2, 64.09, 64.07, 63.0, 27.0, 20.1, 19.5; **IR** (CH_2Cl_2): 3071, 3049, 2959, 2931, 2891, 2858, 1589, 1487, 1428, 1111, 823, 701 cm^{-1}; **HRMS** (NSI) calculated for $C_{22}H_{28}O_2NaSi^+$ $[M+Na]^+$ 375.1751, found 375.1749.

*Preparation of (R,R)-epoxyalkenyl TBDPS ether **21***: Epoxy alcohol **19** (2.64 g, 23.2 mmol) was dissolved in CH_2Cl_2 (80 mL), and cooled to 0 °C. Et_3N (5 mL, 36 mmol) was added followed by TBDPSCl (6.5 mL, 25 mmol) and DMAP (311 mg, 2.5 mmol). The mixture was allowed to warm to rt over 3.5 h, and was quenched with saturated aqueous NH_4Cl (100 mL). The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL), the combined organic layers were washed with water (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified via column chromatography eluting with 5/95 Et_2O/Hexanes to give silyl ether **21** as a clear oil (7.18 g, 88% yield). $[\alpha]_D^{20}$ = -3.8 (CH_2Cl_2, *c* = 0.95); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 7.71-7.68 (m, 4H), 7.47-7.37 (m, 6H), 5.75 (ddd, *J* = 17.3, 10.4, 7.1 Hz, 1H), 5.44 (ddd, *J* = 17.2, 1.6, 0.8 Hz, 1H), 5.36 (ddd, *J* = 10.5, 1.6, 0.7 Hz, 1H), 3.72-3.65 (dd, *J* = 16.1, 11.3 Hz, 2H), 3.35 (d, *J* = 7.2 Hz, 1H), 1.32 (s, 3H), 1.07 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 135.9, 135.8, 133.6, 133.5, 133.2, 129.95, 127.94, 127.93, 120.5, 77.4, 77.2, 77.0, 68.0, 63.0, 61.2, 27.0, 19.5, 14.5; **IR** (neat) 3071, 2959, 2931, 2858, 1589, 1471, 1427, 1113, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{22}H_{28}NaO_2Si^+$ $[M+Na]^+$ 375.1751, found 375.1744.

*Preparation of trimethylsilyl ether **22***: 5-hexen-1-ol (7.0 mL, 52 mmol) was mixed with hexamethyldisilazane (8.5 mL, 40.7 mmol) without solvent, and NBS (461 mg, 2.6 mmol) was added. The mixture was heated to 50 °C for 1.5 h, diluted with pentane and filtered through a pad of SiO_2 (20 g), washing with pentane (200 mL). The eluant was concentrated *in vacuo* at 20 °C to give trimethylsilyl ether **22** as a colorless liquid (8.89 g, 51.6 mmol, 99% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.95 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.08 (q, *J* = 7.1 Hz, 2H), 1.58-1.53 (m, 2H), 1.46-1.41 (m, 2H), 0.12 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 139.1, 114.6, 62.7, 33.8, 32.4, 25.4, -0.2; **IR** (neat): 3078, 2934, 2861, 1641, 1439, 1386, 1250, 1095, 835 cm^{-1}; **HRMS** (APCI) calculated for $C_9H_{21}OSi^+$ $[M+H]^+$ 173.1356, found 173.1353.

*Preparation of trimethylsilyl ether **23***: 6-hepten-1-ol (1.71 g, 14.9 mmol) was mixed with hexamethyldisilazane (2.5 mL, 12.0 mmol) without solvent, and NBS (158 mg, 0.9 mmol) was added. The mixture was heated to 50 °C for 70 min, diluted with pentane and filtered through a pad of SiO_2 (10 g), washing with pentane (200 mL). The eluant was concentrated *in vacuo* at 20 °C to give trimethylsilyl ether **23** as a colorless liquid (2.42 g, 13.0 mmol, 87% yield). **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 5.82 (ddt, *J* = 17.0, 10.3, 6.7 Hz, 1H), 5.01 (ddt, *J* = 17.1, 2.1, 1.6 Hz, 1H), 4.94 (ddt, *J* = 10.2, 2.2, 1.1 Hz, 1H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.06 (q, *J* = 7.3 Hz, 2H), 1.55 (dt, *J* = 14.6, 7.1 Hz, 2H), 1.44-1.38 (m, 2H), 1.37-1.32 (m, 2H), 0.12 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 139.2, 114.5, 62.9, 34.0, 32.8, 29.0, 25.6, -0.2; **IR** (neat): 3078, 2931, 2859, 1641, 1437, 1387, 1250, 1095, 836 cm^{-1}; **HRMS** (APCI) calculated for $C_{10}H_{23}OSi^+$ $[M+H]^+$ 187.1513, found 187.1509.

*Preparation of trimethylsilyl ether **24***: (2-(But-3-en-1-yl)phenyl)methanol (168 mg, 1.03 mmol; prepared from *o*-toluic acid in 2 steps[15b]) was mixed with hexamethyldisilazane (0.25 mL, 1.2 mmol) without solvent, and NBS (9 mg, 0.05 mmol) was added. The mixture was heated to 50 °C for 1 h, diluted with hexanes and filtered through a pad of SiO_2 washing with hexanes. The eluant was concentrated *in vacuo* to give trimethylsilyl ether **24** (204 mg, 0.87 mmol, 84% yield) as a colorless oil. **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.39 (d, *J* = 7.0 Hz, 1H), 7.24-7.18 (m, 3H), 5.91 (ddt, *J* = 17.0, 10.3, 6.6 Hz, 1H), 5.08 (dquintet, *J* = 17.1, 1.7 Hz, 1H), 5.01 (dquintet, *J* = 10.2, 1.3 Hz, 1H), 4.72 (s, 2H), 2.73 (dd, *J* = 8.6, 7.4 Hz, 2H), 2.37 (q, *J* = 7.4 Hz, 2H), 0.17 (s, 9H);

^{13}C-NMR (126 MHz, $CDCl_3$): δ 139.6, 138.5, 138.4, 129.2, 127.9, 127.6, 126.2, 115.1, 62.9, 35.2, 31.8, -0.2; **IR** (CH_2Cl_2): 3078, 3021, 2956, 2871, 1640, 1605, 1490, 1454, 1379, 1251, 1068, 878, 840, 753 cm^{-1}; **HRMS** (NSI) calculated for $C_{14}H_{23}OSi^+$ $[M+H]^+$ 235.1513, found 235.1512.

*Preparation of chiral non-racemic allylic acetate **26***: Racemic alcohol **25** [17] (22.2 g, 96.3 mmol) was dissolved in PhMe (250 mL), and powdered K_3PO_4 (22.4 g, 101 mmol), CAL-B resin (980 mg) and isopropenyl acetate (18.0 mL, 163 mmol) were added. The mixture was stirred for 3.25 hours (^{1}H NMR showed ~50% conversion), filtered through Celite washing with Et_2O, and the eluant concentrated *in vacuo* to give an orange oil. Column chromatography of the crude eluting with 20/80 Et_2O/Hexanes -> 50/50 Et_2O/Hexanes gave the acetate **26** as a clear oil (10.71 g, 41% yield, er 96:4 by analysis of the Mosher ester after hydrolysis of the acetate), and the alcohol (*R*)-**13** as a yellow oil (9.46 g, 43% yield, er 96:4 by analysis of the Mosher ester derivative). The spectra and sign of the optical rotation of **26** matched that reported in the literature.[18a] **$[\alpha]_D^{20}$** = -3.2 (CH_2Cl_2, *c* = 0.69), literature value **$[\alpha]_D^{29}$** = -2.7 (MeOH, *c* = 1.00);[18a] **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.27-5.22 (m, 2H), 5.17 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.65-3.59 (m, 2H), 2.07 (s, 3H), 1.68 (q, *J* = 7.3 Hz, 2H), 1.61-1.50 (m, 2H), 0.90 (s, 9H), 0.05 (s, 6H); **IR** (CH_2Cl_2) 2930, 2954, 2858, 1742, 1472, 1371, 1239, 1099, 835, 776 cm^{-1}.

A sample of (*S*)-**25** was generated by hydrolyzing a sample of acetate **26** (100 mg, 0.37 mmol) with K_2CO_3 (5 mg) in methanol (0.3 M), and heating this mixture to 35 °C on the rotovap bath, monitoring by TLC until acetate **26** was consumed, within 2 h. The mixture was concentrated *in vacuo*, the resulting residue was triturated with Et_2O, and filtered through a small plug of silica gel, providing (*S*)-**25** with ^{1}H NMR spectra identical to *rac*-**25**. Mosher esters were prepared from (*S*)-**25** using the general procedure (vide supra).

*Preparation of (S)-allylic acetate-primary alcohol **27*:** The silyl ether **26** (4.0 g, 17.3 mmol) was dissolved in MeOH (30 mL), cooled to 0 °C, and acetyl chloride (AcCl, 0.35 mL, 4.9 mmol) was added dropwise. After 20 min, saturated aqueous $NaHCO_3$ (10 mL) was added, and the resulting suspension was concentrated *in vacuo* to remove the MeOH. The remaining solution was extracted with Et_2O (3 x 20 mL), the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated *in vacuo* to give a pale yellow oil. The oil was purified via column chromatography eluting with 70/30 Et_2O/Hexanes to give alcohol **27** as a pale yellow oil (1.77 g, 65% yield). **$[\alpha]_D^{20}$** = -11.3 (CH_2Cl_2, *c* = 0.78); **^{1}H-NMR** (400 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.1, 10.6, 6.5 Hz, 1H), 5.29-5.24 (m, 2H), 5.18 (dt, *J* = 10.5, 1.1 Hz, 1H), 3.67 (q, *J* = 5.1 Hz, 2H), 2.07 (s, 3H), 1.77-1.54 (m, 5H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 170.7, 136.4, 117.1, 74.7, 62.6, 30.7, 28.3, 21.5; **IR** (neat) 3398, 2945, 2871, 1736, 1647, 1373, 1242 cm^{-1}; **HRMS** (NSI) calculated for $C_8H_{14}O_3Na^+$ $[M+Na]^+$ 181.0835, found 181.0833.

*Preparation of (S)-allylic acetate trimethylsilyl ether **28***: The alcohol **27** (646 mg, 4.1 mmol) was mixed with hexamethyldisilazane (0.85 mL, 4.1 mmol) without solvent, and NBS (44 mg, 0.25 mmol) was added. The mixture was heated to 50 °C for 1 h, diluted with pentane and filtered through a pad of SiO_2 (10 g) with 5/95 Et_2O/pentane (100 mL). The eluant was concentrated *in vacuo* to give trimethylsilyl ether **28** as a colorless oil (813 mg, 86% yield). **$[\alpha]_D^{20}$** = -2.8 (CH_2Cl_2, *c* = 0.58); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 5.78 (ddd, *J* = 17.2, 10.6, 6.5 Hz, 1H), 5.28-5.23 (m, 2H), 5.18 (dt, *J* = 10.5, 1.2 Hz, 1H), 3.61-3.57 (m, 2H), 2.07 (s, 3H), 1.68-1.66 (m, 2H), 1.59-1.54 (m, 2H), 0.11 (s, 9H); **^{13}C-NMR** (125 MHz; $CDCl_3$): δ 170.6, 136.7, 116.9, 74.8, 62.3, 30.8, 28.4, 21.5, -0.3; **IR** (neat) 2956, 1741, 1371, 1249, 1095, 841 cm^{-1}; **HRMS** (NSI) calculated for $C_{11}H_{22}O_3NaSi^+$ $[M+Na]^+$ 253.1230, found 253.1224.

*Preparation of (R,R)-epoxy-cis-alkenyl trimethylsilyl ether **34***: To a stirred solution of (*R,R*)-epoxyalkene **21** (366 mg, 1.04 mmol) and alkene trimethylsilyl ether **22** (550 mg, 3.2 mmol) in THF (2 mL) was added Grubbs *Z* catalyst **31** (15.4 mg, 0.024 mmol). The solution was heated at 35 °C for 5 h whereupon a solution of additional Grubbs Z catalyst (13.6 mg, 0.021 mmol) in THF (1 mL) was added. The solution was stirred at 35 °C for another 19 h and then concentrated *in vacuo*. Chromatography of the resulting oil eluting with 5/95 Et_2O/hexanes gave (*R,R*)-epoxy-*cis*-alkenyl trimethylsilyl ether **34** as a colorless oil (124 mg, 0.25 mmol, 24% yield, *cis:trans* 90:10). **$[\alpha]_D^{20}$** = -10.5 (CH_2Cl_2, *c* = 0.84); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.38 (m, 4H), 5.77 (dtd, *J* = 11.1, 7.6, 1.0 Hz, 1H), 5.29 (ddt, *J* = 11.2, 8.2, 1.5 Hz, 1H), 3.71-3.67 (m, 2H), 3.65 (dd, *J* = 8.1, 0.9 Hz, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.27-2.14 (m, 2H), 1.59-1.54 (m, 2H), 1.50-1.43 (m, 2H), 1.33 (s, 3H), 1.08 (s, 9H), 0.11 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 137.2, 135.86, 135.80, 133.56, 133.48, 129.9, 127.93, 127.92, 124.7, 68.0, 62.69, 62.62, 56.7, 32.5, 27.9, 27.0, 26.1, 19.5, 15.1, -0.2; **IR** (CH_2Cl_2): 3071, 3049, 2999, 2931, 2896, 2858, 1590, 1473, 1428, 1250, 1113, 841, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{29}H_{45}O_3Si_2^+$ $[M+H]^+$ 497.2902, found 497.2898.

*Preparation of (S,S,R)-epoxyalkenyl trimethylsilyl ether **35***: (*S,R*)-Epoxyalkene **20** (350 mg, 0.99 mmol) and the alkene-trimethylsilyl ether-acetate **28** (464 mg, 2.01 mmol) were dissolved in $CDCl_3$ (2 mL). The Grela catalyst **30** (24.3 mg, 0.036 mmol) was added. The solution was stirred at 35 °C for 0.5 h, then concentrated *in vacuo* (~7 torr) at 35 °C for another 0.5 h. The crude oil was chromatographed on SiO_2 eluting with 20/80 Et_2O/Hexanes to furnish the epoxyalkene-trimethylsilyl ether-acetate **35** as a colorless oil (335 mg, 0.60 mmol, 61% yield). **$[\alpha]_D^{20}$** = +0.1 (CH_2Cl_2, *c* = 0.48); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.46-7.38 (m, 6H), 5.75 (ddd, *J* = 15.6, 6.7, 0.9 Hz, 1H), 5.49 (ddd, *J* = 15.6, 6.8, 1.1 Hz, 1H), 5.22 (q, *J* = 6.3 Hz, 1H), 3.66-3.62 (m, 2H), 3.53-3.48 (m, 2H), 3.27 (d, *J* = 6.7 Hz, 1H), 2.00 (s, 3H), 1.61-1.43 (m, 7H), 1.07 (s, 9H), 0.10 (s, 9H); **^{13}C-NMR** (151 MHz; $CDCl_3$): δ 170.3, 135.85, 135.78, 134.4, 133.5, 133.3, 130.0, 127.93, 127.91, 126.9, 73.5, 65.2, 63.16, 63.14, 62.2, 30.9, 28.3, 27.0, 21.4, 20.1, 19.5, -0.3; **IR** (neat) 2956, 2859, 1740, 1473, 1428, 1373, 1239, 1110, 841, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{31}H_{47}O_5Si_2^+$ $[M+H]^+$ 555.2957, found 555.2955.

*Preparation of (S,R,R)-epoxyalkenyl trimethylsilyl ether **36***: To a solution of (*R,R*)-epoxyalkene **21** (260 mg, 0.74 mmol) and the alkene-trimethylsilyl ether-acetate **28** (341 mg, 1.48 mmol) in $CDCl_3$ (2 mL) was added Grela catalyst **30** (18.7 mg, 0.028 mmol). The solution was stirred at 35 °C for 0.5 h, then concentrated *in vacuo* (~7 torr) at 35 °C for another 0.5 h. NMR of the crude mixture showed complete consumption of the epoxide. The crude oil was chromatographed on SiO_2 eluting with 20/80 Et_2O/Hexanes to furnish the epoxyalkene-trimethylsilyl ether-acetate **36** as a colorless oil (223 mg, 0.40 mmol, 54% yield). **$[\alpha]_D^{20}$** = -9.7 (CH_2Cl_2, *c* = 0.59); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.80 (ddd, *J* = 15.6, 6.6, 0.8 Hz, 1H), 5.61 (ddd, *J* = 15.6, 6.9, 1.1 Hz, 1H), 5.32 (q, *J* = 6.3 Hz, 1H), 3.68 (dd, *J* = 16.9, 11.4 Hz, 2H), 3.60 (td, *J* = 6.4, 1.6 Hz, 2H), 3.36 (d, *J* = 6.9 Hz, 1H), 2.07 (s, 3H), 1.72-1.68 (m, 2H), 1.64-1.50 (m, 2H), 1.27 (s, 3H), 1.06 (s, 9H), 0.12 (s, 9H); **^{13}C-NMR** (151 MHz; $CDCl_3$): δ 170.4, 135.9, 135.8, 134.3, 133.5, 133.4, 130.0, 127.94, 127.93, 127.5, 73.7, 67.5, 63.2, 62.3, 59.9, 31.8, 31.0, 28.4, 27.0, 21.4, 19.5, -0.3; **IR** (neat) 2956, 2859, 1740, 1473, 1429, 1372, 1239 cm^{-1}; **HRMS** (NSI) calculated for $C_{31}H_{47}O_5Si_2^+$ $[M+H]^+$ 555.2957, found 555.2959.

*Preparation of (R,R)-epoxyalkene **37***: To a solution of (*R,R*)-epoxyalkene **21** (352 mg, 1.0 mmol) and 1-hexene (1.00 mL, 8.0 mmol) in $CDCl_3$ (1 mL) was added Grela catalyst **30** (17.2 mg, 0.026 mmol). The solution was concentrated *in vacuo* (~7 torr) at 50 °C for 1 h. The resulting oil was passed through a plug of SiO_2 (10 g) eluting with 5/95 Et_2O/hexanes (100 mL) and the eluent

concentrated *in vacuo* to give (*R,R*)-epoxyalkene **37** as a thick oil (385 mg, 0.94 mmol, 94% yield, *trans:cis* 88:12). **$[\alpha]_D^{20}$** = +6.5 (CH_2Cl_2, *c* = 1.03); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71-7.66 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.38 (m, 4H), 5.88 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.34 (ddt, *J* = 15.4, 7.9, 1.5 Hz, 1H), 3.67 (app. q, *J* = 11.2 Hz, 2H), 3.30 (d, *J* = 7.9 Hz, 1H), 2.11 (qd, *J* = 7.3, 1.2 Hz, 2H), 1.43-1.31 (m, 7H), 1.07 (s, 9H), 0.92 (t, *J* = 7.2 Hz, 3H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 138.1, 135.68, 135.60, 133.39, 133.35, 129.7, 127.70, 127.68, 124.4, 68.0, 62.6, 61.1, 32.3, 31.2, 26.8, 22.2, 19.3, 14.5, 13.9; **IR** (CH_2Cl_2): 2071, 2049, 2998, 2957, 2929, 2857, 1665, 1589, 1472, 1428, 1112, 823, 701 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{37}O_2Si^+$ $[M+H]^+$ 409.2568, found 409.2559.

*Preparation of (R,R)-epoxyalkene trimethylsilyl ether **38***: To a solution of (*R,R*)-epoxyalkene **21** (379 mg, 1.07 mmol) and the alkene trimethylsilyl ether **23** (611 mg, 3.3 mmol) in $CDCl_3$ (3 mL) was added Grela catalyst **30** (14.9 mg, 0.022 mmol). The solution was heated to 35 °C for 2 h, whereupon NMR of a small aliquot indicated ca. 60% conversion to the desired product. Additional metathesis catalyst (10.3 mg, 0.054 mmol) was then added and the reaction heated another 1.5 h at 35 °C. The reaction mixture was then concentrated *in vacuo* and the resulting oil chromatographed eluting with 5/95 Et_2O/Hexanes to furnish compound (*R,R*)-epoxyalkene trimethylsilyl ether **38** as a colorless oil (247 mg, 0.48 mmol, 45% yield, *trans:cis* 90:10). **$[\alpha]_D^{20}$** = +7.4 (CH_2Cl_2, *c* = 0.49); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.42 (m, 2H), 7.41-7.37 (m, 4H), 5.87 (dtd, *J* = 15.4, 6.9, 0.5 Hz, 1H), 5.34 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 3.67 (app. q, *J* = 10.8 Hz, 2H), 3.58 (t, *J* = 6.7 Hz, 2H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.11 (q, *J* = 6.8 Hz,2H), 1.57-1.52 (m, 2H), 1.46-1.40 (m, 2H), 1.38-1.33 (m, 2H), 1.33 (s, 3H), 1.07 (s, 9H), 0.12 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 138.1, 135.9, 135.8, 133.61, 133.56, 129.9, 127.92, 127.90, 124.7, 68.1, 62.83, 62.81, 61.2, 32.79, 32.77, 29.1, 27.0, 25.6, 19.5, 14.7, -0.2; **IR** (CH_2Cl_2): 3071, 3049, 2998, 2956, 2931, 2858, 1590, 1473, 1250, 1106, 840, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{30}H_{47}O_3Si_2^+$ $[M+H]^+$ 511.3058, found 511.3054.

*Preparation of (R,R)-epoxyalkene trimethylsilyl ether **39***: To a solution of (*R,R*)-epoxyalkene **21** (151 mg, 0.43 mmol) and alkenyl silyl ether **24** (197 mg, 0.84 mmol) in $CDCl_3$ (1 mL) was added Grela catalyst **30** (3.9 mg, 0.0058 mmol). The solution was stirred for 1 h whereupon NMR of a small aliquot indicated ca. 60% conversion to the desired product. An additional amount of Grela catalyst (4.9 mg, 0.0073 mmol) was then added and the reaction stirred at rt for another 2 h. NMR of the crude reaction mixture then showed high (>90%) conversion to the desired cross metathesis product. The reaction mixture was concentrated *in vacuo* and the resulting oil chromatographed eluting with 5/95 Et_2O/hexanes to give *(R,R)*-epoxyalkene trimethylsilyl ether **39** as a colorless oil (173 mg, 0.31 mmol, 72%, *trans:cis* 89:11). **$[\alpha]_D^{20}$** = +5.1 (CH_2Cl_2, *c* = 0.48); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 5H), 7.24-7.19 (m, 2H), 7.18-7.16 (m, 1H), 5.95 (dtd, *J* = 15.4, 6.8, 0.5 Hz, 1H), 5.40 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 4.71 (s, 2H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.65 (d, *J* = 11.3 Hz, 1H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.80-2.70 (m, 2H), 2.44-2.39 (m, 2H), 1.32 (s, 3H), 1.07 (s, 9H), 0.17 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 139.4, 138.5, 137.1, 135.9, 135.8, 133.58, 133.55, 129.9, 129.3, 128.1, 127.93, 127.91, 127.7, 126.4, 125.4, 68.1, 62.93, 62.88, 61.1, 34.0, 31.9, 27.0, 19.5, 14.7, -0.2; **IR** (CH_2Cl_2): 3071, 3049, 3021, 2957, 2931, 2896, 2858, 1737 (weak), 1589, 1487, 1428, 1251, 1113, 1074, 873, 841, 742, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{34}H_{47}O_3Si_2^+$ $[M+H]^+$ 559.3058, found 559.3027.

*Preparation of (S,R)-epoxyalkenyl alcohol **40***: To a solution of (*S,R*)-epoxyalkene **20** (349 mg, 0.99 mmol) and the alkene trimethylsilyl ether **22** (683 mg, 3.96 mmol) in $CDCl_3$ (2 mL) was added Grela catalyst **30** (21 mg, 0.051 mmol). The solution was stirred at rt under active argon flow for 1 h, then concentrated *in vacuo* at 35 °C for 0.5 hours. The resulting oil was chromatographed on SiO_2 eluting with 5/95 Et_2O/hexanes to furnish the trimethylsilyl-protected

product **32** as a colorless oil (361 mg, 0.73 mmol, 74% yield). The oil was dissolved in MeOH (1.4 mL) and cooled to 0 °C whereupon K_2CO_3 (11.2 mg, 0.081 mmol) was added. After 1 h, the reaction mixture was concentrated *in vacuo*, diluted with Et_2O and filtered through a small pipette containing SiO_2 (~1 g). The resulting solution was concentrated *in vacuo* to give (*S,R*)-epoxyalkenyl alcohol **40** as a clear oil (293 mg, 70% yield over 2 steps, *trans:cis* 90:10). **$[\alpha]_D^{20}$** = +10.6 (CH_2Cl_2, *c* = 0.53); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.70-7.66 (m, 4H), 7.46-7.37 (m, 6H), 5.82 (dt, *J* = 15.3, 7.0 Hz, 1H), 5.21 (ddt, *J* = 15.4, 7.5, 1.4 Hz, 1H), 3.67 (dd, *J* = 26.7, 10.9 Hz, 2H), 3.60 (q, *J* = 5.7 Hz, 2H), 3.25 (d, *J* = 7.4 Hz, 1H), 2.03 (q, *J* = 7.3 Hz, 2H), 1.54-1.50 (m, 2H), 1.41-1.35 (m, 2H), 1.19-1.17 (m, 1H), 1.07 (s, 9H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 137.3, 135.86, 135.79, 133.6, 133.4, 129.92, 129.91, 127.90, 127.87, 124.6, 65.5, 64.1, 62.93, 62.86, 32.4, 27.0, 25.2, 20.2, 19.5; **IR** (neat) 3419, 3070, 2932, 2858, 1472, 1428, 1111, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.2326, found 447.2319.

*Preparation of (R,R)-epoxyalkenyl alcohol **41***: To a solution of (*R,R*)-epoxyalkene **21** (1.72 g, 4.9 mmol) and the alkene trimethylsilyl ether **22** (2.52 g, 14.6 mmol) in $CDCl_3$ (10 mL) was added Grela catalyst **30** (34 mg, 0.051 mmol). The solution was heated to 40 °C for 1 h, whereupon NMR of a small aliquot indicated 60% conversion to the desired product. At 1.5 hours, a solution of additional Grela catalyst **30** (36 mg, 0.054 mmol) in $CDCl_3$ was added. At 3.5 hours, NMR of an aliquot showed the presence of ethylene (singlet ca. 5.4 ppm) dissolved in the reaction mixture. Argon was then bubbled through the reaction mixture to displace the ethylene, with an aliquot at 4.5 h showing *ca*. 67% conversion to the desired product **33**. The reaction mixture was concentrated *in vacuo* and the resulting oil chromatographed eluting with 5/95 Et_2O/hexanes to furnish the trimethylsilyl-protected product **33** as a colorless oil (996 mg, 2.0 mmol, 41% yield). This product was immediately dissolved in MeOH (4 mL) and cooled to 0 °C whereupon K_2CO_3 (32 mg, 0.23 mmol) was added. After 1 h, the reaction mixture was concentrated *in vacuo*, diluted with Et_2O and filtered through a small pipette containing SiO_2 (~1 g). The resulting solution was concentrated *in vacuo* to give (*R,R*)-epoxyalkenyl alcohol **41** as a clear oil (879 mg, 41% yield over 2 steps, *trans:cis* 89:11). **$[\alpha]_D^{20}$** = +5.4 (CH_2Cl_2, *c* = 0.65); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 5.88 (dt, *J* = 15.4, 6.9 Hz, 1H), 5.36 (dd, *J* = 15.4, 7.9 Hz, 1H), 3.69-3.63 (m, 4H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.15 (q, *J* = 7.2 Hz, 2H), 1.63-1.58 (m, 2H), 1.53-1.47 (m, 2H), 1.33 (s, 3H), 1.25-1.22 (m, 1H), 1.07 (s, 9H); **^{13}C-NMR** (101 MHz; $CDCl_3$): δ 137.7, 135.88, 135.79, 133.54, 133.50, 129.9, 127.92, 127.90, 125.1, 68.0, 62.99, 62.86, 61.1, 32.51, 32.40, 27.0, 25.4, 19.5, 14.7; **IR** (neat) 3392, 3071, 2931, 2858, 1590, 1472, 1427, 1112, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_3Si$ $[M+Na]^+$ 447.2326, found 447.2319.

*Preparation of (R,R)-epoxy-cis-alkenyl alcohol **42***: To a stirred solution of (*R,R*)-epoxy-*cis*-alkenyl trimethylsilyl ether **34** (83 mg, 0.16 mmol) in MeOH (2 mL) at rt was added solid NH_4Cl (97 mg, 1.8 mmol). The mixture was stirred for 5 h and then the solvent removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* and then chromatographed eluting with 50/50 Et_2O/hexanes to 75/25 Et_2O/hexanes to give (*R,R*)-epoxy-*cis*-alkenyl alcohol **42** as a colorless oil (56 mg, 0.13 mmol, 83% yield, *cis:trans* 90:10). **$[\alpha]_D^{20}$** = -13.4 (CH_2Cl_2, *c* = 1.19); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.70-7.68 (m, 4H), 7.46-7.43 (m, 2H), 7.42-7.38 (m, 4H), 5.78 (dtd, *J* = 11.1, 7.6, 0.9 Hz, 1H), 5.31 (ddt, *J* = 11.1, 8.1, 1.5 Hz, 1H), 3.72-3.67 (m, 2H), 3.67-3.64 (m, 3H), 2.29-2.16 (m, 2H), 1.63-1.57 (m, 2H), 1.53-1.48 (m, 2H), 1.33 (s, 3H), 1.30 (s, 1H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 137.0, 135.85, 135.78, 133.54, 133.46, 129.9, 127.93, 127.91, 124.8, 68.0, 62.9, 62.7, 56.7, 32.4, 27.8, 27.0, 25.9, 19.5, 15.1; **IR** (CH_2Cl_2): 3405, 3071, 2048, 2998, 2931, 2858, 1589, 1462, 1428, 1113, 823, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{37}O_3Si^+$ $[M+H]^+$ 425.2507, found 425.2510.

*Preparation of (S,S,R)-epoxyalkenyl diol **43***: To a stirred solution of epoxyalkene-trimethylsilyl ether-acetate **35** (92 mg, 0.16 mmol) in MeOH (2 mL) was added K_2CO_3 (6.4 mg, 0.046 mmol). The mixture was stirred at rt for 3.5 h and concentrated *in vacuo* to give a residue which was dissolved in Et_2O (5 mL). The resulting solution was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Concentration of the Et_2O solution gave a crude oil which was purified by preparatory thin layer chromatography eluting with 5/95 MeOH/CH_2Cl_2 to give (*S,S,R*)-epoxyalkenyl diol **43** as a viscous oil (37.1 mg, 0.084 mmol, 53% yield, *trans:cis* > 98:2, dr 86:14 (±2)). **$[\alpha]_D^{20}$** = +10.2 (CH_2Cl_2, *c* = 1.005); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.70-7.65 (m, 4H), 7.44 (ddt, *J* = 9.4, 5.2, 1.8 Hz, 2H), 7.42-7.38 (m, 4H), 5.81 (ddd, *J* = 15.5, 6.2, 0.9 Hz, 1H), 5.43 (ddd, *J* = 15.5, 6.9, 1.3 Hz, 1H), 4.08-4.03 (m, 1H), 3.71-3.57 (m, 4H), 3.28 (d, *J* = 6.8 Hz, 1H), 2.21-1.92 (m, 2H), 1.64-1.52 (m, 4H), 1.51 (s, 3H), 1.06 (s, 9H); **^{13}C-NMR** (125 MHz; $CDCl_3$): δ 139.4, 135.88, 135.79, 133.50, 133.42, 130.0, 127.94, 127.93, 125.3, 72.1, 67.8, 66.1, 63.16, 63.09, 60.3, 34.4, 28.9, 27.0, 19.5, 15.5, 14.7; **IR** (CH_2Cl_2) 3365, 3071, 2931, 2858, 1471, 1428, 1111, 703 cm^{-1}; **HRMS** (NSI, negative ion mode) calculated for $C_{26}H_{35}O_4Si^-$ $[M-H]^-$ 439.2310, found 439.2314.

*Preparation of (S,R,R)-epoxyalkenyl diol **44***: To a stirred solution of epoxyalkene-trimethylsilyl ether-acetate **36** (97 mg, 0.17 mmol) in MeOH (2 mL) was added K_2CO_3 (6.5 mg, 0.047 mmol). The mixture was stirred at rt for 3.5 h and concentrated *in vacuo* to give a residue which was dissolved in Et_2O (5 mL). The resulting solution was washed with water (2 x 5 mL), brine (5 mL) and dried over Na_2SO_4. Concentration of the Et_2O solution gave a crude oil which was purified by preparatory thin layer chromatography eluting with Et_2O to give (*S,R,R*)-epoxyalkenyl diol **44** as a viscous oil (41.0 mg, 0.093 mmol, 55% yield, *trans:cis* >98:2, dr 88:12 (±2)). **$[\alpha]_D^{20}$** = +8.0 (CH_2Cl_2, *c* = 0.993); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.93 (ddd, *J* = 15.6, 5.9, 0.6 Hz, 1H), 5.62 (ddd, *J* = 15.5, 7.5, 1.3 Hz, 1H), 4.27-4.24 (m, 1H), 3.73-3.65 (m, 4H), 3.36 (d, *J* = 7.5 Hz, 1H), 2.34-2.33 (m, 1H), 2.02-1.89 (m, 1H), 1.77-1.63 (m, 4H), 1.32 (s, 3H), 1.07 (s, 9H); **^{13}C-NMR** (125 MHz; $CDCl_3$): δ 139.4, 135.88, 135.79, 133.50, 133.42, 130.0, 127.94, 127.93, 125.3, 72.1, 67.8, 66.1, 63.16, 63.09, 60.3, 34.4, 28.9, 27.0, 19.5, 15.5, 14.7; **IR** (CH_2Cl_2) 3365, 3071, 2930, 2857, 1471, 1428, 1112, 703 cm^{-1}; **HRMS** (NSI, negative ion mode) calculated for $C_{26}H_{35}O_4Si^-$ $[M-H]^-$ 439.2310, found 439.2315.

*Preparation of (S,S,R)-epoxyalkene hydroxy acetate **45***: To a stirred solution of epoxyalkene-trimethylsilyl ether-acetate **35** (208 mg, 0.37 mmol) in MeOH (3.7 mL) at rt was added solid NH_4Cl (200 mg, 3.7 mmol). The mixture was stirred for 3 h and then the solvent was removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo*, and the resulting oil purified by preparatory thin layer chromatography eluting with Et_2O to give (*S,S,R*)-epoxyalkene hydroxy acetate **45** as a colorless oil (143 mg, 0.296 mmol, 80% yield, *trans:cis* 96:4, dr of *trans* 85:15 (±2)). **$[\alpha]_D^{20}$ =** -1.8 (CH_2Cl_2, *c* = 0.998); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.71-7.65 (m, 4H), 7.46-7.39 (m, 6H), 5.73 (ddd, *J* = 15.6, 6.8, 0.9 Hz, 1H), 5.52 (ddd, *J* = 15.6, 6.5, 1.1 Hz, 1H), 5.21 (q, *J* = 6.4 Hz, 1H), 3.65 (d, *J* = 1.8 Hz, 2H), 3.55 (t, *J* = 6.3 Hz, 2H), 3.28 (d, *J* = 6.4 Hz, 1H), 2.01 (s, 3H), 1.64-1.58 (m, 1H), 1.56-1.51 (m, 1H), 1.49 (s, 3H), 1.48-1.40 (m, 2H), 1.07 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 170.4, 135.84, 135.75, 134.0, 133.5, 133.3, 129.96, 129.95, 127.92, 127.90, 127.2, 73.5, 65.2, 63.2, 63.0, 62.4, 30.8, 28.3, 26.9, 21.4, 20.0, 19.5; **IR** (CH_2Cl_2): 3449, 3071, 2931, 2858, 1737, 1428, 1373, 1239, 1111, 704 cm^{-1}; **HRMS** (NSI, negative ion mode) calculated for $C_{28}H_{37}O_5Si^-$ $[M-H]^-$ 481.2416, found 481.2421.

*Preparation of (S,R,R)-epoxyalkene hydroxy acetate **46***: To a stirred solution of (*S,R,R*)-epoxyalkene trimethylsilyl ether acetate **36** (78 mg, 0.14 mmol) in MeOH (1.4 mL) at rt was added

solid NH_4Cl (80 mg, 1.5 mmol). The mixture was stirred for 3 h and then the solvent was removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g) (note: for this run some of the material was irretrievably spilled). The resulting eluant was concentrated *in vacuo*, and the resulting oil purified by preparatory thin layer chromatography eluting with Et_2O to give (*S,R,R*)-epoxyalkene hydroxy acetate **46** as a colorless oil (29.9 mg, 0.296 mmol, 44% yield, *trans:cis* >98:2, dr 92:8 (±2)). **$[\alpha]_D^{20}$ =** -13.3 (CH_2Cl_2, *c* = 1.005); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m,4H), 5.81 (ddd, *J* = 15.6, 6.5, 0.8 Hz, 1H), 5.63 (ddd, *J* = 15.6, 6.8, 1.2 Hz, 1H), 5.34 (q, *J* = 6.7 Hz, 1H), 3.69-3.68 (m, 4H), 3.36 (d, *J* = 6.8 Hz, 1H), 2.07 (s, 3H), 1.78-1.70 (m, 2H), 1.66-1.59 (m, 2H), 1.42 (m, 1H), 1.28 (s, 3H), 1.07 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 170.5, 135.87, 135.77, 134.1, 133.49, 133.40, 130.0, 127.94, 127.93, 127.7, 73.6, 67.6, 63.2, 62.6, 59.8, 30.9, 28.4, 27.0, 21.4, 19.5, 14.5; **IR** (CH_2Cl_2): 3425, 3071, 2931, 2858, 1737, 1427, 1239, 1112, 704 cm^{-1}; **HRMS** (NSI) calculated for $C_{28}H_{39}O_5Si^+$ $[M+H]^+$ 483.2561, found 483.2565.

*Preparation of (R,R)-epoxyalkenyl alcohol **47***: To a stirred solution of (*R,R*)-epoxyalkenyl trimethylsilyl ether **38** (191 mg, 0.37 mmol) in MeOH (3.8 mL) at rt was added solid NH_4Cl (417 mg, 7.8 mmol). The mixture was stirred for 5 h, and then the solvent was removed *in vacuo*. The resulting residue was triturated extensively with Et_2O and the triturate filtered through a small pipette of SiO_2 (1 g). The resulting eluant was concentrated *in vacuo* and then chromatographed eluting with 50/50 Et_2O/hexanes to 75/25 Et_2O/hexanes to give (*R,R*)-epoxyalkenyl alcohol **47** as a colorless oil (144 mg, 0.33 mmol, 88% yield, *trans:cis* 83:17). **$[\alpha]_D^{20}$** = +5.1 (CH_2Cl_2, *c* =0.35); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.70-7.67 (m, 4H), 7.45-7.42 (m, 2H), 7.41-7.38 (m, 4H), 5.87 (dtd, *J* = 15.4, 6.9, 0.5 Hz, 1H), 5.35 (ddt, *J* = 15.4, 7.8, 1.5 Hz, 1H), 3.69-3.62 (m, 4H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.12 (qd, *J* = 7.2, 1.2 Hz, 2H), 1.62-1.57 (m, 2H), 1.47-1.38 (m, 4H), 1.33 (s, 3H), 1.22 (s, 1H), 1.07 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 137.9, 135.9, 135.8, 133.60, 133.56, 129.9, 127.92, 127.90, 124.9, 68.1, 63.2, 62.9, 61.2, 32.82, 32.75, 29.0, 27.0, 25.5, 19.5, 14.7; **IR** (CH_2Cl_2): 3370, 3070, 3049, 2998, 2931, 2857, 1665, 1589, 1428, 1113, 824, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{27}H_{39}O_3Si^+$ $[M+H]^+$ 439.2663, found 439.2667.

*Preparation of (R,R)-epoxyalkenyl alcohol **48***: To a solution of (*R,R*)-epoxyalkenyl trimethylsilyl ether **39** (164 mg, 0.29 mmol) in MeOH (1 mL) at 0 °C was added K_2CO_3 (10.3 mg, 0.075 mmol). After 1 h, the reaction mixture was concentrated *in vacuo*, triturated with Et_2O and the triturate filtered through a small pipette containing SiO_2 (~1 g) eluting with Et_2O. The resulting solution was concentrated *in vacuo* to give (*R,R*)-epoxyalkenyl alcohol **48** as a colorless oil (140 mg, 0.28 mmol, 99% yield, *trans:cis* 89:11). **$[\alpha]_D^{20}$** = +10.6 (CH_2Cl_2, *c* = 0.60); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.69-7.67 (m, 4H), 7.46-7.42 (m, 2H), 7.42-7.37 (m, 5H), 7.28-7.19 (m, 3H), 5.94 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.39 (ddt, *J* = 15.5, 7.8, 1.4 Hz, 1H), 4.74 (d, *J* = 5.8 Hz, 2H), 3.69 (d, *J* = 11.2 Hz, 1H), 3.64 (d, *J* = 11.3 Hz, 1H), 3.30 (d, *J* = 7.8 Hz, 1H), 2.81 (dd, *J* = 8.8, 7.3 Hz, 2H), 2.45-2.41 (m, 2H), 1.54 (t, *J* = 5.8 Hz, 1H), 1.31 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 139.9, 138.9, 136.9, 135.9, 135.8, 133.6, 133.5, 129.9, 129.7, 128.6, 128.3, 127.93, 127.91, 126.6, 125.6, 68.1, 63.4, 62.9, 61.1, 34.3, 32.0, 27.0, 19.5, 14.7; **IR** (CH_2Cl_2): 3402, 3070, 3049, 3027, 2998, 2957, 2930, 2892, 2857, 1589, 1428, 1112, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{31}H_{39}O_3Si^+$ $[M+H]^+$ 487.2674, found 487.2660.

Cycloisomerizations with $PhSO_3H$ catalysis:

*From (S,R)-epoxyalkenyl alcohol **40***: A solution of (*S,R*)-epoxyalkenyl alcohol **40** (10.8 mg, 0.025 mmol) in $CDCl_3$ (0.5 mL) in a clean NMR tube was treated with a solution of $PhSO_3H$ (0.40 mg, 0.0025 mmol) in $CDCl_3$ (0.18 mL). The reaction mixture was monitored by ^{1}H NMR. After 5 min the reaction had gone to >90% completion (by integration with respect to the TBDPS

tert-butyl group). The diastereomer ratio (**49:50**, determined by ^{1}H NMR integration) was 70:30 favoring (*S,S*)-pyranyl alcohol **49**.

*From (R,R)-epoxyalkenyl alcohol **41***: By a similar procedure, a solution of (*R,R*)-epoxyalkenyl alcohol **41** (10.3 mg, 0.025 mmol) in $CDCl_3$ (0.6 mL) was treated with $PhSO_3H$ (0.12 mg, 0.00075 mmol) in $CDCl_3$ (0.1 mL). After 2.5 h the substrate **41** was completely consumed. The reaction mixture was poured over solid $NaHCO_3$ (~50 mg) and filtered through a small plug of SiO_2 eluting with Et_2O, giving predominantly (*R,S*)-pyranyl alcohol **50** as a colorless film (8.9 mg, 0.022 mmol, 82:18 dr, 87% isolated yield).

*From (R,R)-epoxy-cis-alkenyl alcohol **42***: By a similar procedure, a solution of (*R,R*)-epoxy-*cis*-alkenyl alcohol **42** (10.3 mg, 0.025 mmol) in $CDCl_3$ (0.6 mL) was treated with $PhSO_3H$ (0.12 mg, 0.00075 mmol) in $CDCl_3$ (0.1 mL). After 3.5 h the substrate **42** was completely consumed. The reaction mixture was poured over solid $NaHCO_3$ (~50 mg) and filtered through a small plug of SiO_2 eluting with Et_2O, giving predominantly (*S,S*)-pyranyl alcohol **49** as a colorless film (9.3 mg, 0.023 mmol, 83:17 dr, 90% isolated yield).

*From (S,S,R)-epoxyalkenyl diol **43***: By a similar procedure, a solution of epoxyalkenyl diol **43** (10.3 mg, 0.023 mmol) in $CDCl_3$ (0.8 mL) was treated with $PhSO_3H$ (0.36 mg, 0.0023 mmol) in $CDCl_3$ (0.1 mL). After 2 h the reaction had gone to ~50% completion (by integration with respect to the TBDPS *tert*-butyl group). The diastereomer ratio of pyran products (**54:55**, determined by ^{1}H NMR integration) was 63:37 favoring (*S,R*)-pyranyl diol **54**.

*From (S,R,R)-epoxyalkenyl diol **44***: By a similar procedure, a solution of epoxyalkenyl diol **44** (12.9 mg, 0.029 mmol) in $CDCl_3$ (0.8 mL) was treated with $PhSO_3H$ (0.46 mg, 0.0029 mmol) in $CDCl_3$ (0.1 mL). After 2 h the reaction had gone to >90% completion, giving a diastereomer ratio of 85:15 favoring (*S,S*)-pyranyl diol **55**.

*From (S,S,R)-epoxyalkenyl hydroxy acetate **45***: By a similar procedure, a solution of epoxyalkene hydroxy acetate **45** (14.0 mg, 0.029 mmol) in $CDCl_3$ (0.5 mL) was treated with $PhSO_3H$ (0.44 mg, 0.0028 mmol) in $CDCl_3$ (0.2 mL). After 2.5 h, the reaction had gone to >90% completion. The diastereomer ratio (**56**:**57**, determined by ^{1}H NMR integration) was 74:26 favoring (*S,R,S*)-pyran hydroxy acetate **56**.

*From (S,R,R)-epoxyalkenyl hydroxy acetate **46***: By a similar procedure, a solution of epoxyalkene hydroxy acetate **46** (13.2 mg, 0.027 mmol) in $CDCl_3$ (0.5 mL) was treated with $PhSO_3H$ (0.44 mg, 0.0028 mmol) in $CDCl_3$ (0.2 mL). After 2.5 h the reaction had gone to >90% completion, giving a diastereomer ratio of 83:17 favoring (*S,S,S*)-pyran hydroxy acetate **57**.

*Reaction of (R,R)-epoxyalkene **37** with $PhSO_3H$:* To a solution of (*R,R*)-epoxyalkene **37** (21.6 mg, 0.053 mmol) in $CDCl_3$ (0.7 mL) was added anhydrous $PhSO_3H$ (3.5 mg, 0.022 mmol). The solution was transferred to a clean NMR tube and monitored by ^{1}H NMR. Note: We found that a large, but sub-stoichiometric, amount of acid was optimal for obtaining a high concentration of allylic benzenesulfonate intermediate **52** in solution. If a stoichiometric amount was used, the products decomposed too rapidly for NMR analysis. If too little benzenesulfonic acid was used, the amount of **52** present in solution was not amenable to facile interrogation by NMR. Because of the high rate of reaction observed between benzenesulfonic acid and epoxy alkenes such as **37**, any acid present in solution will quickly react with it. Decomposition of the intermediate **52** will release the acid back into solution, which will quickly react with another equivalent of epoxyalkene **37**. Thus, a steady amount of **52** is generated for NMR analysis over several hours of spectrometer time. Attempts to quench and isolate allylic benzenesulfonate **52** were frustrated by rapid degradation. After 5 h, intermediate **52** had been completely consumed, with (*E,E*)- and (*Z,E*)-dienes **53** observed by NMR.

We observed that the allylic benzenesulfonate intermediate **52** was produced as a mixture of diastereomers. Irradiation of the resonance at 4.97 ppm in a 1D-TOCSY experiment revealed an extended spin system. Heteronuclear correlation experiments showed that the proton resonance at 4.97 ppm was correlated to two carbons at 84 ppm, presumably representing both

diastereomers of the allyl benzenesulfonate. Attempts at observing a long range heteronuclear coupling between H_b and the *ipso* carbon of the benzenesulfonate were unsuccessful. The large concentration of **52** in solution allowed for NOE correlations to be measured, revealing correlations between H_a on the benzenesulfonate with H_b, H_c and H_d (see Figure 11).

Cycloisomerizations with Pd-triisopropyl phosphite catalysis:

*From (S,R)-epoxyalkenyl alcohol **40***: To a solution of (*S,R*)-epoxyalkenyl alcohol **40** (182 mg, 0.43 mmol) in CH_2Cl_2 (4 mL) was added $Ph_2P(O)OH$ (10.5 mg, 0.048 mmol) and P(O-*i*-Pr)$_3$ (32 μL, 0.131 mmol), followed by $Pd(PPh_3)_4$ (25.3 mg, 0.022 mmol) at rt. After 2 h, saturated aqueous $NaHCO_3$ (1 mL) was added, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 x 1 mL). The combined organics were dried over Na_2SO_4 and concentrated *in vacuo* to give an orange oil. ^{1}H NMR of the crude product mixture showed no traces of **40**, and the dr was 88:12 (**49**:**50**). Chromatography of the crude product mixture on SiO_2 eluting with 50/50 Et_2O/hexanes furnished (*S,S*)-pyranyl alcohol **49** as a colorless oil (153 mg, 0.36 mmol, 84% yield).

*From (R,R)-epoxyalkenyl alcohol **41***: By a similar procedure, a solution of (*R,R*)-epoxyalkenyl alcohol **41** (131 mg, 0.31 mmol) in CH_2Cl_2 (3 mL) was treated with $Ph_2P(O)OH$ (7.5 mg, 0.034 mmol) and P(O-*i*-Pr)$_3$ (23 μL, 0.094 mmol), followed by $Pd(PPh_3)_4$ (18.8 mg, 0.016 mmol) at rt. TLC showed the reaction to be complete after 15 min. A similar workup provided a crude product mixture, with ^{1}H NMR analysis showing no traces of substrate **47**, and dr of 85:15 (**50**:**49**). Chromatographic purification as above furnished (*R,S*)-pyranyl alcohol **50** as a colorless oil (115 mg, 0.27 mmol, 88% yield).

Preparation of Pd-catalyst solution: $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) was dissolved in dry CH_2Cl_2 (5 mL). To this solution was added P(O-*i*-Pr)$_3$ (37 μL, 0.15 mmol) followed by $Ph_2P(O)OH$ (11 mg, 0.05 mmol). The yellow-orange solution was then agitated in a sonicator. Note: the phosphinic acid does not all dissolve, thus is important to homogenize the solution as much as possible prior to removing an aliquot.

*From (S,S,R)-epoxyalkenyl diol **43***: A vial was charged with (*S,R*)-epoxyalkenyl diol **43** (19.1 mg, 0.043 mmol), and Pd catalyst solution as prepared above was added (0.45 mL). The reaction mixture was stirred at rt for 0.75 h (judged complete by TLC), and then concentrated *in vacuo*. ^{1}H NMR of the crude product mixture showed trace of starting material. Preparative thin layer chromatography of the crude eluting with 5/95 MeOH/CH_2Cl_2 gave (*S,R*)-pyranyl diol **54** as a colorless film (8.6 mg, 0.019 mmol, 45% yield, 94:6 dr) and enone **58** as a colorless film (6.1 mg, 0.013 mmol, 31% yield).

*From (S,S,R)-epoxyalkenyl hydroxy acetate **45***: By a similar procedure, (*S,S,R*)-epoxyalkenyl hydroxy acetate **45** (37 mg, 0.077 mmol), and Pd catalyst solution was added (0.45 mL). The reaction mixture was stirred at rt for 1.5 h (judged complete by TLC), and then concentrated *in vacuo*. ^{1}H NMR of the crude product mixture showed >90% conversion to product with respect to the TBDPS *tert*-butyl group. Preparative thin layer chromatography of the crude product eluting with Et_2O gave (*S,R,S*)-pyran hydroxy acetate **56** as a colorless film (18.3 mg, 0.038 mmol, 49% yield) and enone **58** as a colorless film (4.3 mg, 0.009 mmol, 12% yield).

*From (S,R,R)-epoxyalkenyl hydroxy acetate **46***: By a similar procedure, epoxyalkene hydroxy acetate **46** (18.8 mg, 0.039 mmol) was treated with Pd catalyst solution (0.38 mL). After 2 h, the reaction was judged complete by TLC, and ^{1}H NMR of the crude product mixture showed >90% conversion to product. Preparative TLC gave (*S,S,S*)-pyran hydroxy acetate **56** as a colorless film (1 mg, 0.002 mmol, 5% yield) and (*S,R,S*)-pyran hydroxy acetate **57** as a colorless film (10.7 mg, 0.022 mmol, 57% yield).

*From (R,R)-epoxyalkenyl alcohol **48***: A solution of (*R,R*)-epoxyalkenyl alcohol **48** (13.7 mg, 0.028 mmol) in $CDCl_3$ (0.7 mL) was treated with $Ph_2P(O)OH$ (1 mg, 0.004 mmol), P(O-*i*-Pr)$_3$ (8 μL, 0.033 mmol) and $Pd(PPh_3)_4$ (5.8 mg, 0.005 mmol) at rt. NMR after 35 min showed a ratio

of starting material to cyclization product of (22:78). TLC after 2 h showed complete disappearance of epoxyalkenyl alcohol **48**. The reaction mixture was purified by preparative TLC eluting with 50/50 Et_2O/hexanes to give benzooxepane alcohol **60** as a colorless oil (5.8 mg, 0.012 mmol, 42% yield, dr of 87:13).

Cycloisomerizations with Pd-trimethylolpropane phosphite (EtCage) catalysis:

*From (S,R)-epoxyalkenyl alcohol **40***: To a solution of (*S,R*)-epoxyalkenyl alcohol **40** (17.9 mg, 0.042 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was added a solution of $Ph_2P(O)OH$ (1.9 mg, 0.009 mmol), trimethylolpropane phosphite (EtCage, **61**, 4.5 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (4.9 mg, 0.004 mmol) in $CDCl_3$ (0.3 mL) at rt. After 3 h, the reaction had proceeded to ~65% conversion to (*S,S*)-pyranyl alcohol **49**. After 22 h, substrate **40** had been consumed, with (*S,S*)-pyranyl alcohol **49** as the only identifiable product by NMR.

*From (R,R)-epoxyalkenyl alcohol **47***: To a solution of (*R,R*)-epoxyalkenyl alcohol **47** (83:17 *trans*:*cis*, 18.7 mg, 0.043 mmol) in $CDCl_3$ (0.7 mL) in an NMR tube was added a solution of $Ph_2P(O)OH$ (1.9 mg, 0.009 mmol), trimethylolpropane phosphite (EtCage, **61**, 4.5 mg, 0.028 mmol) and $Pd(PPh_3)_4$ (4.9 mg, 0.004 mmol) at rt. After 24 hours, oxepane alcohol **59** was observed in greater than 90% conversion by NMR (with respect to the *tert*-butyl group of the TBDPS). The remaining material (~10%) was identified as 10-((*tert*-butyldiphenylsilyl)oxy)-9-methyldeca-5,7-diene-1,9-diol, as a mixture of *cis*- and *trans*-diene isomers. The reaction mixture was purified by preparative TLC eluting with 50/50 Et_2O/hexanes to give oxepane alcohol **59** as a colorless oil (4.7 mg, 0.011 mmol, 25% isolated yield, dr of 82:18).

*Characterization of (S,S)-pyranyl alcohol **49***: $[\alpha]_D^{20}$ = -15.5 (CH_2Cl_2, *c* = 0.78); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.68-7.64 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.37 (m, 4H), 5.78 (dd, *J* = 15.8, 5.4 Hz, 1H), 5.72 (dd, *J* = 15.8, 1.1 Hz, 1H), 4.03 (ddt, *J* = 11.5, 4.0, 1.9 Hz, 1H), 3.80 (dddd, *J* = 11.0, 5.4, 2.2, 1.0 Hz, 1H), 3.55-3.46 (m, 3H), 2.62 (s, 1H), 1.88-1.83 (m, 1H), 1.66 (dtt, *J* = 13.5, 2.9, 2.1 Hz, 1H), 1.63-1.49 (m, 3H), 1.39 (tdd, *J* = 12.6, 11.1, 3.7 Hz, 1H), 1.27 (s, 3H), 1.08-1.07 (m, 9H); **^{13}C-NMR** (125 MHz; $CDCl_3$): δ 135.85, 135.80, 134.5, 133.27, 133.21, 130.9, 130.0, 127.95, 127.93, 77.9, 73.0, 71.3, 68.6, 32.4, 27.1, 26.1, 24.4, 23.6, 19.6; **IR** (neat) 3429, 3071, 2932, 2857, 1589, 1472, 1428, 1362, 1203, 1110, 1084, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.2326, found 447.2328.

*Characterization of (R,S)-pyranyl alcohol **50***: $[\alpha]_D^{20}$ = -17.8 (CH_2Cl_2, *c* = 0.72); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.68-7.65 (m,4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m, 4H), 5.79 (dd, *J* = 15.8, 5.1 Hz, 1H), 5.71 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.03 (ddt, *J* = 11.5, 4.0, 1.9 Hz, 1H), 3.82 (dddd, *J* = 11.0, 5.1, 2.2, 1.3 Hz, 1H), 3.55-3.47 (m, 3H), 2.63 (s, 1H), 1.87-1.83 (m, 1H), 1.65 (dddt, *J* = 12.3, 4.3, 2.3, 2.0 Hz, 1H), 1.62-1.49 (m, 3H), 1.40-1.32 (m, 1H), 1.27 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (125 MHz; $CDCl_3$): δ 135.88, 135.81, 134.1, 133.28, 133.20, 130.8, 130.0, 127.95, 127.93, 77.7, 73.0, 71.2, 68.6, 32.3, 27.1, 26.1, 24.5, 23.7, 19.5**; IR** (neat) 3442, 3071, 2932, 2857, 1590 1472, 1428, 1361, 1110, 1084, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_3Si^+$ $[M+Na]^+$ 447.2326, found 447.2332.

*Determination of absolute stereochemistry of pyran center in **50***: (*R,S*)-Pyranyl alcohol **50** (97 mg, 0.23 mmol) was dissolved in CH_2Cl_2 (3 mL) and MeOH (3 mL) and the solution cooled to -78 °C. Ozone was bubbled through the solution for 5 min, whereupon the solution turned blue. O_2 was then bubbled through the solution until it decolorized (5 min). After warming to 0 °C, $NaBH_4$ (93 mg, 2.46 mmol) was added to the solution slowly in portions. The mixture was stirred for 2 h whereupon water (5 mL) was added. The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 x 3 mL). The combined organics were dried over anhydrous KCl and concentrated *in vacuo*. The resulting residue was purified by preparatory thin layer

chromatography, eluting with Et_2O to furnish tetrahydropyranylmethanol **51** as a colorless film (8.0 mg, 0.069 mmol, 30%). Spectral data matched that reported in the literature.[6] The sign of the optical rotation was opposite that described by Lemieux for the enantiomer arising from deoxygenation of D-galactose,[24] allowing for the assignment of the pyran center of our synthetic **51** as (*R*).

Characterization of (S,R,S)-pyranyl diol ***54***: **$[\alpha]_D^{20}$ =** -4.6 (CH_2Cl_2, *c* = 0.683); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.68-7.64 (m, 4H), 7.47-7.38 (m, 6H), 5.89 (d, *J* = 15.8 Hz, 1H), 5.84 (dd, *J* = 15.7, 6.5 Hz, 1H), 3.95 (ddt, *J* = 11.2, 4.0, 1.9 Hz, 1H), 3.56-3.47 (m, 5H), 3.39 (td, *J* = 11.1, 3.6 Hz, 1H), 3.30 (dddd, *J* = 11.2, 8.3, 5.0, 3.1 Hz, 1H), 2.68 (s, 1H), 2.15 (dqd, *J* = 12.4, 4.1, 1.3 Hz, 1H), 1.86 (d, *J* = 3.2 Hz,1H), 1.45 (tdd, *J* = 12.4, 10.6, 5.3 Hz, 1H), 1.28 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 138.8, 135.82, 135.80, 133.10, 133.05, 130.11, 130.10, 128.0, 127.4, 83.4, 73.1, 71.3, 70.0, 67.7, 31.6, 27.1, 25.6, 24.3, 19.5; **IR** (CH_2Cl_2) 3374, 3052, 2930, 2856, 1462, 1437, 1112, 1090, 701, 541 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.2275, found 463.2272.

Characterization of (S,S,S)-pyranyl diol ***55***: **$[\alpha]_D^{20}$ =** -12.0 (CH_2Cl_2, *c* = 0.508); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.67-7.64 (m, 4H), 7.44 (ddt, *J* = 8.4, 6.2, 1.8 Hz, 2H), 7.41-7.38 (m, 4H), 5.86 (dd, *J* = 15.8, 1.3 Hz, 1H), 5.80 (dd, *J* = 15.8, 4.2 Hz, 1H), 4.04 (ddt, *J* = 11.3, 4.4, 2.1 Hz, 1H), 3.95 (dt, *J* = 4.1, 1.2 Hz, 1H), 3.70 (m, 1H), 3.56-3.51 (m,3H), 2.62 (s, 1H), 2.04-1.93 (m, 2H), 1.86 (d, *J* = 5.7 Hz, 1H), 1.69 (tdd, *J* = 13.2, 4.4, 2.5 Hz, 1H), 1.39 (ddt, *J* = 13.6, 4.5, 2.3 Hz, 1H), 1.27 (d, *J* = 4.2 Hz, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 136.7, 135.85, 135.84, 133.18, 133.16, 130.1, 128.0, 127.1, 79.5, 73.3, 71.3, 68.6, 66.8, 30.1, 27.1, 24.6, 20.2, 19.5; **IR** (CH_2Cl_2) 3411, 2929, 2855, 1464, 1427, 1107, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.2275, found 463.2268.

Characterization of (S,R,S)-pyran hydroxy acetate **56**: **$[\alpha]_D^{20}$ =** -2.6 (CH_2Cl_2, *c* = 0.983); **^{1}H-NMR** (600 MHz; $CDCl_3$): δ 7.65 (dd, *J* = 6.7, 0.8 Hz, 4H), 7.46-7.42 (m, 2H), 7.41-7.38 (m, 4H), 5.83 (dd, *J* = 15.8, 0.9 Hz, 1H), 5.73 (dd, *J* = 15.8, 6.2 Hz, 1H), 4.57 (ddd, *J* = 10.5, 9.1, 4.6 Hz, 1H), 3.96 (ddt, *J* = 11.3, 4.1, 2.0 Hz, 1H), 3.70 (ddd, *J* = 9.1, 6.3, 0.8 Hz, 1H), 3.50 (q, *J* = 10.2 Hz, 2H), 3.42 (td, *J* = 11.3, 3.2 Hz, 1H), 2.57 (s, 1H), 2.17 (dqd, *J* = 12.5, 4.1, 1.2 Hz, 1H), 1.94 (s, 3H), 1.79-1.69 (m, 2H), 1.51 (tdd, *J* = 12.3, 10.7, 4.9 Hz, 1H), 1.27 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 170.3, 138.7, 135.84, 135.80, 133.24, 133.16, 130.04, 130.03, 127.98, 127.96, 126.7, 80.0, 73.0, 71.8, 71.2, 67.5, 29.3, 27.1, 25.1, 24.4, 21.4, 19.6; **IR** (CH_2Cl_2) 3466, 3071, 2931, 2857, 1740, 1472, 1428, 1239, 1106, 1082, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{28}H_{38}NaO_5Si^+$ $[M+Na]^+$ 505.2381, found 505.2373.

Characterization of (S,S,S)-pyran hydroxy acetate **57**: **$[\alpha]_D^{20}$ =** -16.2 (CH_2Cl_2, *c* = 0.925); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.65 (dd, *J* = 8.0, 1.4 Hz, 4H), 7.46-7.42 (m, 2H), 7.40-7.37 (m, 4H), 5.75 (d, *J* = 15.8 Hz, 1H), 5.72 (dd, *J* = 15.9, 3.5 Hz, 1H), 4.91-4.89 (q, *J* = 2.8 Hz, 1H), 4.07 (ddt, *J* = 11.5, 4.3, 2.0 Hz, 1H), 3.99 (dd, *J* = 3.5, 1.7 Hz, 1H), 3.55 (td, *J* = 11.8, 2.4 Hz, 1H), 3.50-3.46 (m, 2H), 2.56 (s, 1H), 2.01 (ddq, *J* = 13.6, 3.9, 2.5 Hz, 1H), 1.95 (s, 3H), 1.90 (qt, *J* = 13.2, 4.3 Hz, 1H), 1.75 (tdd, *J* = 13.7, 4.3, 3.1 Hz, 1H), 1.44 (dtt, *J* = 12.3, 3.5, 2.4 Hz, 1H), 1.26 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 170.8, 136.00, 135.85, 135.82, 133.25, 133.22, 130.0, 127.97, 127.96, 126.7, 78.2, 73.1, 71.3, 69.4, 68.0, 27.9, 27.1, 24.6, 21.2, 20.9, 19.6; **IR** (CH_2Cl_2) 3467, 3070, 3953, 2930, 2857, 1736, 1241, 1087, 704 cm^{-1}; **HRMS** (NSI) calculated for $C_{28}H_{38}NaO_5Si^+$ $[M+Na]^+$ 505.2381, found 505.2374.

Characterization of enone ***58***: **$[\alpha]_D^{20}$ =** -9.1 (CH_2Cl_2, *c* = 0.550); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.66-7.65 (m, 4H), 7.47-7.45 (m, 2H), 7.42-7.39 (m, 4H), 6.88 (ddd, *J* = 15.9, 8.1, 7.1 Hz, 1H),

6.13 (dt, *J* = 15.9, 1.3 Hz, 1H), 3.67 (q, *J* = 4.5 Hz, 2H), 3.48 (s, 2H), 2.68 (td, *J* = 6.9, 1.3 Hz, 2H), 2.53 (ddd, *J* = 14.1, 7.0, 1.4 Hz, 1H), 2.49 (s, 1H), 2.36 (ddd, *J* = 14.1, 8.1, 1.2 Hz, 1H), 1.88 (tt, *J* = 6.9, 6.1 Hz, 2H), 1.84-1.80 (m, 1H), 1.16 (s, 3H), 1.10 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 200.7, 143.3, 135.8, 133.4, 132.97, 132.94, 130.20, 130.18, 128.1, 72.9, 70.8, 62.6, 42.1, 36.8, 27.1, 27.0, 23.7, 19.6; **IR** (CH_2Cl_2) 3413, 3071, 2958, 2030, 2857, 1663, 1828, 1427, 1110, 821, 703 cm^{-1}; **HRMS** (NSI) calculated for $C_{26}H_{36}NaO_4Si^+$ $[M+Na]^+$ 463.2275, found 463.2273.

*Characterization of oxepane alcohol **59***: **$[\alpha]_D^{20}$** = -18.7 (CH_2Cl_2, *c* = 0.35); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.68-7.65 (m, 4H), 7.46-7.43 (m, 2H), 7.41-7.38 (m, 4H), 5.78 (dd, *J* = 15.7, 5.0 Hz, 1H), 5.69 (dd, *J* = 15.7, 1.4 Hz, 1H), 4.07 (dtd, *J* = 9.0, 4.5, 1.3 Hz, 1H), 3.83 (ddd, *J* = 12.4, 6.8, 4.0 Hz, 1H), 3.60 (ddd, *J* = 12.3, 7.6, 3.9 Hz, 1H), 3.54 (d, *J* = 9.7 Hz, 1H), 3.50 (d, *J* = 9.7 Hz, 1H), 2.61 (s, 1H), 1.86 (dddd, *J* = 11.5, 7.1, 4.5, 2.4 Hz, 1H), 1.80-1.71 (m, 2H), 1.70-1.63 (m, 2H), 1.60-1.51 (m, 3H), 1.26 (s, 3H), 1.08 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 135.9, 135.8, 133.4, 133.31, 133.26, 131.5, 130.0, 127.97, 127.95, 79.1, 73.0, 71.4, 67.9, 36.1, 31.4, 27.4, 27.1, 25.6, 24.6, 19.6; **IR** (CH_2Cl_2): 3424, 3071, 3050, 2998, 2929, 2857, 1671, 1590, 1472, 1112, 823, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{27}H_{39}O_3Si^+$ $[M+H]^+$ 439.2663, found 439.2673.

*Characterization of benzooxepane alcohol **60***: **$[\alpha]_D^{20}$** = -8.8 (CH_2Cl_2, *c* = 0.42); **^{1}H-NMR** (600 MHz, $CDCl_3$): δ 7.67-7.63 (m, 4H), 7.45-7.36 (m, 4H), 7.35-7.32 (m, 2H), 7.22-7.15 (m, 4H), 5.83 (dd, *J* = 15.8, 5.1 Hz, 1H), 5.74 (dd, *J* = 15.8, 1.3 Hz, 1H), 4.74 (d, *J* = 13.7 Hz, 1H), 4.73 (d, *J* = 13.8 Hz, 1H), 4.28 (dddd, *J* = 10.3, 5.1, 2.2, 1.4 Hz,1H), 3.52 (d, *J* = 9.8 Hz, 1H), 3.50 (d, *J* = 9.7 Hz, 1H), 3.11 (ddd, *J* = 14.5, 12.4, 1.8 Hz, 1H), 2.91 (ddd, *J* = 14.9, 7.0, 1.7 Hz, 1H), 2.61 (s, 1H), 1.97 (ddt, *J* = 14.2, 7.0, 2.1 Hz, 1H), 1.64 (dddd, *J* = 14.1, 12.2, 10.3, 1.8 Hz, 1H), 1.26 (s, 3H), 1.07 (s, 9H); **^{13}C-NMR** (151 MHz, $CDCl_3$): δ 142.3, 140.0, 135.9, 135.8, 134.3, 133.3, 133.2, 130.7, 130.01, 129.99, 129.3, 128.6, 128.1, 128.0, 127.9, 126.4, 84.5, 73.4, 73.0, 71.3, 35.2, 34.2, 27.1, 24.5, 19.6; **IR** (CH_2Cl_2): 3565, 3450, 3070, 3047, 3019, 2998, 2930, 2856, 1671, 1428, 1374, 1112, 1082, 823, 702 cm^{-1}; **HRMS** (NSI) calculated for $C_{31}H_{39}O_3Si^+$ $[M+H]^+$ 487.2674, found 487.2660.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.

Mechanistic proposal for decomposition of products **54** and **55**
Mechanistic proposal for generation of enone byproduct **58**
NMR spectra of purified substrates and products (PDF)

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Notes

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(29) The acyclic enone byproduct **58** may have resulted from an η^3-η^1 slip of π-allyl complex **63** (see Figure 12), followed by *beta*-hydride elimination and tautomerization. The *beta*-hydride elimination may be disfavored in reactive intermediates arising from substrates **45** and **46**, due to the electron-withdrawing nature of acetoxy substituents. A mechanistic proposal for the formation of enone **57** is described in the Supporting Information.

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