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Racemization in Prins Cyclization Reactions

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Abstract: Isotopic labeling experiments were performed to elucidate a new mechanism for racemization in Prins cyclization reactions. The loss in optical activity for these reactions was shown to occur by 2-oxonia-Cope rearrangements by way of a (*Z*)-oxocarbenium ion intermediate. Reaction conditions such as solvent, temperature, and the nucleophile employed played a critical role in whether an erosion in enantiomeric excess was observed. Additionally, certain structural features of Prins cyclization precursors were also shown to be important for preserving optical purity in these reactions.

Introduction

The Prins cyclization[1] is a very powerful synthetic transformation to rapidly assemble tetrahydropyran rings.[2,3] Tetrahydropyran rings are common structural motifs in numerous biologically relevant molecules such as the phorboxazoles,[4] spongistatins,[5] and bryostatins.[6] In fact, several groups have taken advantage of this transformation in elegant approaches to natural product targets.[7] While this reaction has shown great potential for organic synthesis, two deleterious racemization pathways have been previously demonstrated.[8] In this article, we illustrate the existence of a third racemization pathway and elucidate its mechanism.

As with any reaction creating new stereogenic centers, the utility of the Prins cyclization is highly dependent on the degree of stereoselectivity associated with the transformation. Several factors are involved when rationalizing the stereochemical outcome for Prins cyclization reactions. Ring closure of an alkene onto an oxocarbenium ion through a chair transition state leads to tetrahydropyranyl cation intermediate **2**[9] (Figure 1). In this ring-closure step, the C2[10] substituent lies in a favorable equatorial position and the (*E*)-oxocarbenium ion geometry is preferred[11] over the (*Z*)-oxocarbenium ion geometry. Therefore, chirality is transferred from C2 to the newly formed carbon−carbon bond. The stereocenter formed at C4 is controlled by the extensive delocalization of tetrahydropyranyl cation **2**.[9a] Favorable orbital overlap places the hydrogen at C4 in a pseudoaxial geometry, and, therefore, nucleophilic attack occurs

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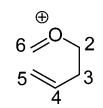

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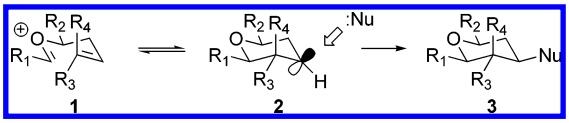

Figure 1. Stereochemical outcome for Prins cyclizations.

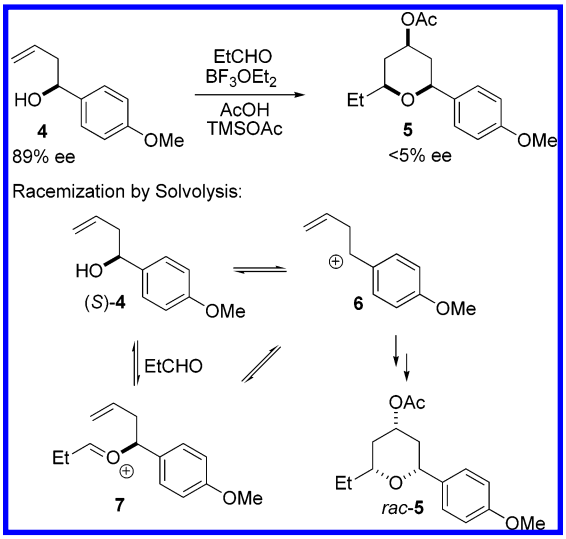

Figure 2. Loss of enantiomeric excess in Prins cyclizations of electron-rich benzylic homoallylic alcohols (Mechanism A).

along an equatorial trajectory to deliver tetrahydropyran **3**.[12] In this way, four stereogenic centers of the tetrahydropyran ring can be formed with high stereoselectivity from one initial stereocenter and a defined alkene geometry.

Another important feature for a synthetically useful transformation is the ability to convert optically active starting materials into optically active products. Although typically proceeding with high stereochemical fidelity, the Prins cyclization reaction has at times been plagued by racemization.[8,13] Willis et al. have demonstrated that Prins cyclizations of benzylic alcohols can lead to an extensive loss in enantiomeric excess by way of a solvolysis mechanism (Figure 2).[8a] For example, treatment of optically enriched alcohol **4** with $BF_3{\cdot}OEt_2$ in the presence of propanal and acetic acid led to tetrahydropyran **5** in less than 5% ee. In this case, stabilized benzylic cation **6** can be generated by a solvolysis reaction of initial alcohol **4** or oxocarbenium ion **7**. This stabilized, achiral benzylic cation then recombines with propanal, ultimately leading to racemic tetrahydropyran **5** (Mechanism A). Due to this solvolysis mechanism, Prins cyclization reactions utilizing electron-rich aromatic substrates are often problematic.[8a]

In addition to the solvolysis pathway shown in Mechanism A, we have previously demonstrated a process for racemization in Prins cyclizations that does not require the presence of an electron-rich aromatic ring. For instance, treatment of optically enriched alcohol **8** with $BF_3{\cdot}OEt_2$ in the presence of hydrocinnamaldehyde and acetic acid led to tetrahydropyran **9** in 67% ee along with symmetric tetrahydropyrans **10** and **11** (Figure 3).[8b] The mechanism for racemization in this case relies on an allyl transfer process. Alcohol (*R*)-**8** can condense with hydrocinnamaldehyde to generate oxocarbenium ion **12** and liberate a molecule of water. Oxocarbenium ion **12** can then undergo a 2-oxonia-Cope rearrangement[14,15] to generate oxocarbenium ion **13**. Readdition of water to oxocarbenium ion **13** leads to a fragmentation process generating benzaldehyde and alcohol (*R*)-**14**. The formation of benzaldehyde and alcohol (*R*)-**14** now allows for a symmetric 2-oxonia-Cope rearrangement. Initial alcohol (*R*)-**8** can condense with benzaldehyde, rearrange via a 2-oxonia-Cope rearrangement, then fragment with the addition of water to generate epimeric (*S*)-**8**. Likewise, alcohol (*R*)-**14** can generate epimeric (*S*)-**14**. In this way, allyl transfer processes can lead to a loss in optical activity for Prins cyclization reactions (Mechanism B). Racemization by Mechanism B is easily identifiable in that it is accompanied by the formation of symmetric tetrahydropyran products (**10** and **11**). Additionally,

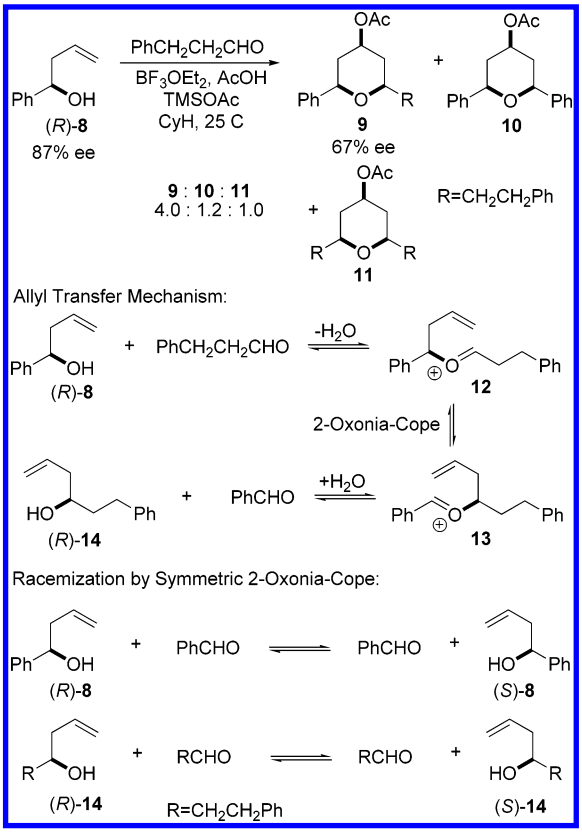

Figure 3. Racemization of Prins cyclization products by symmetric 2-oxonia-Cope rearrangement (Mechanism B).

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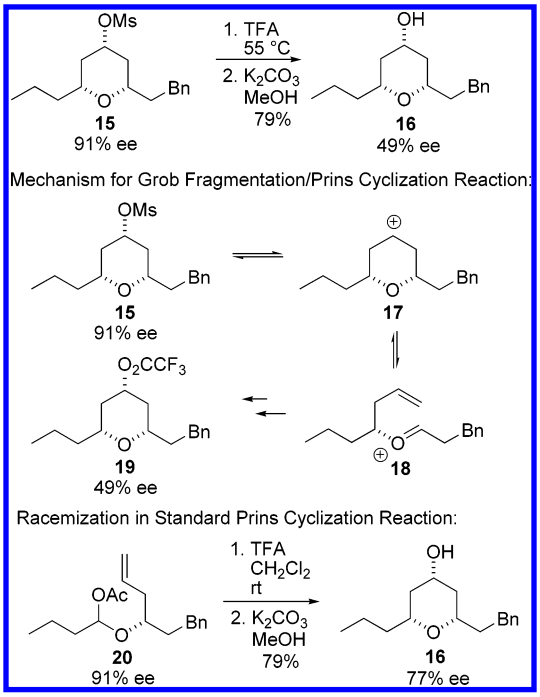

Figure 4. Unusual racemization in Prins cyclizations.

Mechanism B relies on the presence of water. Direct Prins cyclizations utilizing homoallylic alcohols and aldehydes generate water upon condensation. Prins cyclizations of acetoxy ethers, however, do not generate water in situ and therefore can be used to avoid racemization by Mechanism B.

Recently, we observed a loss of enantiomeric excess in a tandem Grob fragmentation/Prins cyclization reaction that does not seem to be consistent with either Mechanism A or B (Figure 4, **15** to **16**).[16] Treatment of mesylate **15** with trifluoroacetic acid initially generates tetrahydropyranyl cation **17**. This cation can then undergo a ring-opening process to generate oxocarbenium ion **18**. Oxocarbenium ion **18** then eventually undergoes a Prins cyclization followed by nucleophilic trapping to deliver tetrahydropyran **19**. Surprisingly, the product of this Grob fragmentation/Prins cyclization pathway had undergone a significant loss in optical activity (91% ee to 49% ee). Furthermore, treatment of acetoxy ether **20** under Prins cyclization conditions promoted by trifluoroacetic acid[17] also led to a significant decrease in enantiomeric excess. In both of these cases, an electron-rich aromatic group is not present as is required for the solvolysis pathway in Mechanism A. Mechanism B also was considered unlikely because symmetric tetrahydropyran products were not observed in either reaction.

In this article, we describe experiments designed to elucidate a third mechanism for racemization in Prins cyclization reactions. We provide evidence that the loss in optical activity is due to rapid 2-oxonia-Cope rearrangements involving a (*Z*)-oxocarbenium ion intermediate. We also demonstrate that reaction conditions such as solvent, temperature, and the nucleophile employed can influence the extent of racemization. In addition, we illustrate that structural features such as the type of alkene employed can also play a critical role in whether the initial enantiomeric excess of the starting material is preserved.

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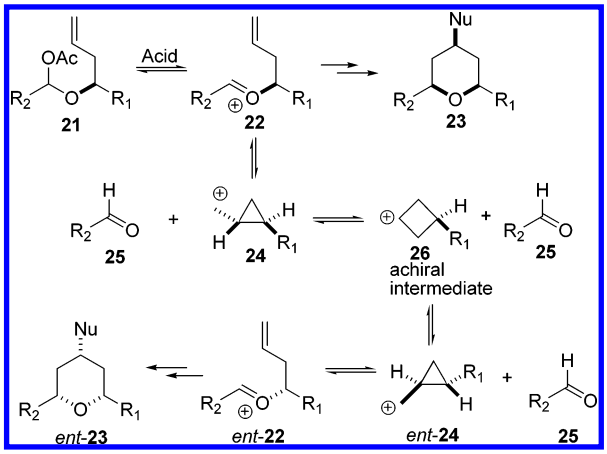

Figure 5. Racemization of Prins cyclization products by achiral cyclobutyl cation intermediate (Mechanism C).

Proposed Mechanisms for Racemization in Prins Cyclization Reactions

At the outset of this study, we considered three additional mechanisms that might lead to a loss in optical activity for Prins cyclization reactions. The first mechanism relies on an achiral cyclobutane intermediate (Mechanism C). Treatment of optically active acetoxy ether **21** with an acid will initially generate oxocarbenium ion **22** (Figure 5). Oxocarbenium ion **22** could then proceed by normal Prins cyclization and nucleophilic termination to deliver optically active tetrahydropyran **23**. Alternatively, oxocarbenium ion **22** could undergo internal displacement by the alkene to generate a chiral cyclopropyl carbinyl cation **24** and expel aldehyde **25**. Racemization may then occur by ring expansion of intermediate **24** to achiral cyclobutyl cation **26**. Cyclobutyl cation **26** then has an equal probability of either a ring contraction leading back to cyclopropyl carbinyl cation **24** or a ring contraction leading to cyclopropyl carbinyl cation *ent*-**24**. By recombining with aldehyde **25**, cation *ent*-**24** could eventually lead to the formation of tetrahydropyran *ent*-**23**. In this way, the formation of cyclobutyl cation **26** would lead to a loss of optical activity in Prins cyclization reactions.

The second mechanism we considered for loss of optical activity in Prins cyclizations is similar to Mechanism A that has already been demonstrated. In this case, homoallylic cation **27** is generated from oxocarbenium ion **22**, but this time the fragmentation process does not rely on the presence of an electron-rich aromatic ring (Figure 6). The reaction conditions shown in Figure 4 in which high concentrations of trifluoroacetic acid were employed may induce solvolysis of an oxocarbenium ion even without a good stabilizing group due to the exceptional solvolytic properties of trifluoroacetic acid.[18] In addition, solvolysis reactions of homoallylic systems have been shown to be accelerated due to stabilization from the alkene.[19] Therefore, the combination of a reaction medium with high solvolytic power and the presence of homoallylic participation may in fact facilitate fragmentation of oxocarbenium ion **22** to homoallylic cation **27** and aldehyde **25** (Mechanism D). Recombination of cation **27** and aldehyde **25** would then be

(18) See the following and references therein: Nordlander, J. E.; Gruetzmacher, R. R.; Kelly, W. J.; Jindal, S. P. *J. Am. Chem. Soc.* **1974**, *96*, 181−185.
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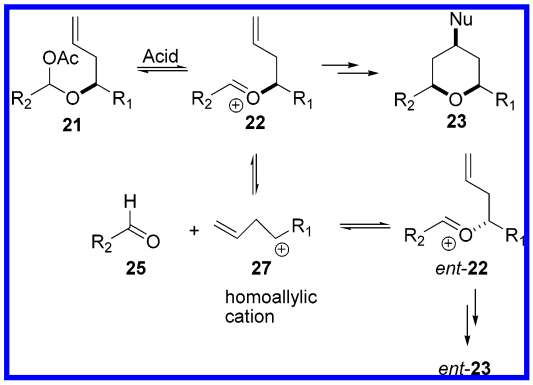


Figure 6. Racemization of Prins cyclization products due to homoallylic cation intermediate (Mechanism D).

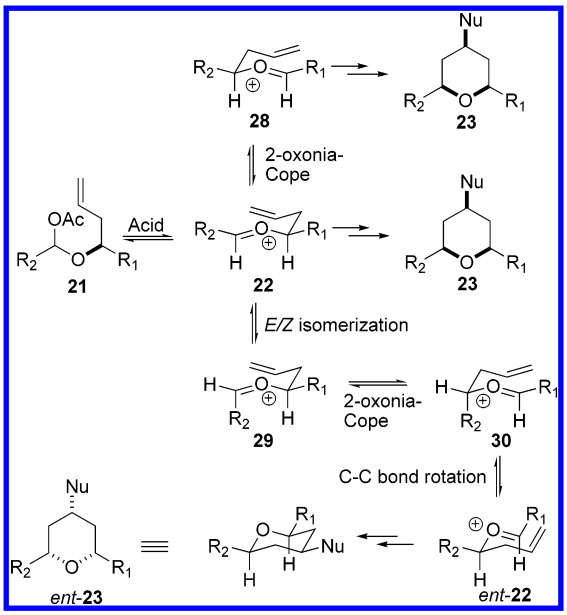


Figure 7. Racemization of Prins cyclization products due to *E*/*Z* isomerization and 2-oxonia-Cope rearrangement (Mechanism E).

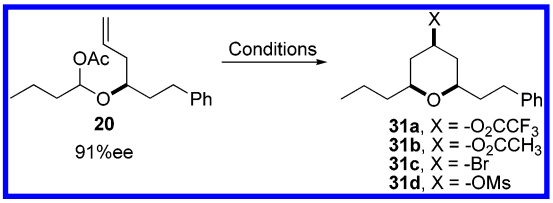
expected to occur in an unselective manner, leading to a loss in enantiomeric excess for Prins cyclization reactions.

The final proposed mechanism relies on unselective 2-oxonia-Cope rearrangements. Typically, an intervening 2-oxonia-Cope rearrangement is not deleterious to the stereochemical outcome of the Prins cyclization reaction. For instance, oxocarbenium ions **22** and **28** will both lead to tetrahydropyran **23** (Figure 7). However, if (*E*)-oxocarbenium ion **22** undergoes an isomerization to (*Z*)-oxocarbenium ion **29**, a 2-oxonia-Cope rearrangement will then lead to oxocarbenium ion **30**. Oxocarbenium ion **30** upon C−C bond rotation can generate oxocarbenium ion *ent*-**22**, which will eventually lead to tetrahydropyran *ent*-**23**. In this way, 2-oxonia-Cope rearrangement proceeding through a (*Z*)-oxocarbenium ion can lead to an erosion of optical purity in Prins cyclization reactions (Mechanism E). A similar pathway for racemization has been suggested for iminium ion cyclizations.[20]

Results

The Effect of Reaction Conditions and Substrate Structure on Loss of Optical Activity in Prins Cyclizations. The loss

Table 1. Effect of Reaction Conditions on Loss of Optical Activity in Prins Cyclizations



entry	Lewis acid	X	solvent	temp (°C)	% yield[a]	% ee **31**[b]
1	TFA	$-O_2CCF_3$[c]	TFA	55	74	66
2	TFA	$-O_2CCF_3$[c]	TFA	25	72	77
3	TFA	$-O_2CCF_3$[c]	TFA	0	73	84
4	TFA[d]	$-O_2CCF_3$[c]	CH_2Cl_2	25	78	84
5	TFA[d]	$-O_2CCF_3$[c]	pentane	25	80	91
6	$BF_3{\cdot}OEt_2$[e]	$-O_2CCH_3$	CH_2Cl_2	25	86	77
7	$SnBr_4$[e]	−Br	CH_2Cl_2	25	75	91
8	TMSOMs[e]	−OMs	CH_2Cl_2	25	30	68
9[f]	TFA	$-O_2CCF_3$[c]	TFA	25	47	71

[a] Yield of product after flash chromatography. [b] Enantiomeric excess determined by HPLC using a Chiracel OD-H column. Authentic racemates were synthesized by cyclization of racemic acetoxy ether. [c] Analysis was conducted after hydrolysis of the trifluoroacetate with K_2CO_3/MeOH. [d] 10 equivalents of TFA was employed. [e] 3 equivalents of Lewis acid was employed. [f] Direct Prins cyclization of corresponding homoallylic alcohol and aldehyde.

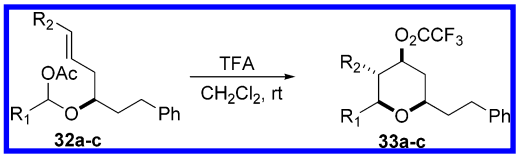
in enantiomeric excess for the Prins cyclization reaction shown in Figure 4 (**20** to **16**) occurred under very specific conditions. We decided to explore the generality of this result by surveying the effect of a wide variety of reaction conditions upon the loss of optical activity in Prins cyclization reactions (Table 1). The acetoxy ethers used for this study were prepared by standard means developed in our laboratory[21] and are further documented in the Supporting Information. Entries 1−3 demonstrate the importance of temperature for the loss of optical activity in Prins cyclizations. Prins cyclization at an elevated temperature (entry 1) resulted in a greater loss in enantiomeric excess than when conducted at lower temperatures (entry 3). Entries 2, 4, and 5 highlight the significance of polarity for the loss of optical activity in Prins cyclization reactions. Entry 2, the most polar reaction conditions, resulted in the greatest loss in enantiomeric excess, whereas the least polar conditions, entry 5, resulted in no loss in enantiomeric excess. The nucleophile employed also proved to be important for the preservation of optical activity in Prins cyclizations. Prins cyclization reaction utililizing a bromide nucleophile (entry 7) proceeded with no loss in enantiomeric excess. In contrast, Prins cyclization terminated by a mesylate nucleophile (entry 8) resulted in tetrahydropyran **31d** in only 68% ee. The last entry in Table 1 demonstrates the difference between a direct Prins cyclization between an aldehyde and alcohol (entry 9) and one utilizing an acetoxy ether (entry 2). Direct Prins cyclization results in a slightly lower optical activity due to symmetric 2-oxonia-Cope rearrangements (Mechanism B, Figure 3). Consistent with this hypothesis, entry 9 was the only Prins cyclization condition that resulted in symmetric tetrahydropyran products (ca. 8%).

In addition to reaction conditions, substrate structure played an important role in whether optical activity was preserved in Prins cyclization reactions (Table 2). By utilizing a chloromethyl substituent (entry 2) as opposed to an alkyl substituent (entry

(20) (a) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919−3930. (b) Castro, P.; Overman, L. E. *Tetrahedron Lett.* **1993**, *34*, 5243−5246.

(21) (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

Table 2. Effect of Substrate Structure on Loss of Optical Activity in Prins Cyclizations

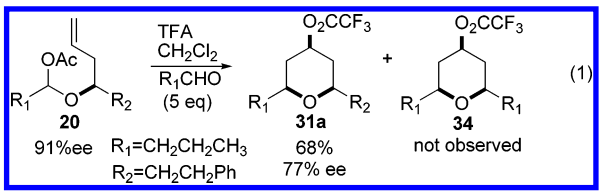


entry[a]	SM	R_1	R_2	% ee **32**[b]	% yield[c]	% ee **33**[d]
1	**32a**	−*n*-propyl	−H	91	70	78
2	**32b**	$-CH_2Cl$	−H	91	62	91
3	**32c**	−*n*-propyl	$-CH_3$	99	82	99

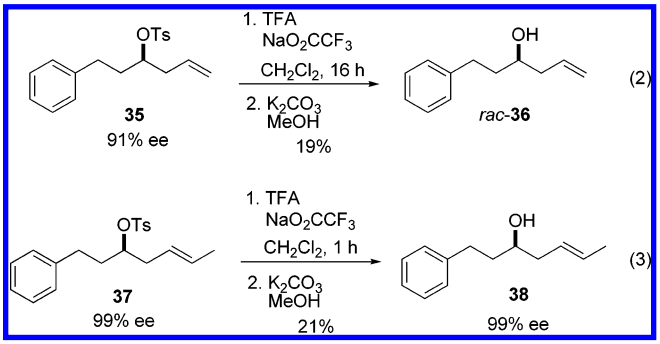
[a] The reaction conditions employed in Table 2 are slightly different from those utilized for entry 4, Table 1. For the entries in Table 2, a 2.5:1 ratio of TFA/CH_2Cl_2 was employed as reported by Willis et al.[17] [b] Enantiomeric excess for acetoxy ethers was established from starting homoallylic alcohols. Alcohols were assayed by either chiral HPLC or GC analysis. [c] Yield of product after flash chromatography. [d] Enantiomeric excess determined by either chiral HPLC or GC analysis.

1), we observed a total retention of enantiomeric excess for Prins cyclizations promoted by trifluoroacetic acid.[17] Likewise, incorporation of a substituted alkene (entry 3) instead of a terminal alkene also led to a total retention of enantiomeric excess. These interesting structural effects will be further addressed in the Discussion.

Exploring the Mechanism for Loss of Optical Activity in Prins Cyclizations. Initially, we investigated the validity of Mechanisms C and D by the simple crossover experiment shown in eq 1. Both Mechanisms C and D rely on a fragmentation/recombination pathway involving a cation and an aldehyde. If either of these mechanisms is operable, Prins cyclization in the presence of an exogenous aldehyde might result in tetrahydropyran products incorporating the aldehyde. Equation 1 clearly demonstrates that this is not the case. Prins cyclization of acetoxy ether **20** in the presence of 5 equiv of butyraldehyde did not produce symmetric tetrahydropyran **34**. This result is consistent with the conclusion that neither Mechanism C nor D is operable and that Mechanism E is the pathway that leads to racemization. Although tempting, we were wary of drawing this conclusion too quickly. Solvent cage effects could potentially render the crossover experiment shown in eq 1 irrelevant. In other words, if recombination occurs faster than escape from the solvent cage, incorporation of a second aldehyde would not be expected. In addition, Mechanism E involves unfavorable (*Z*)-oxocarbenium ion intermediates. We have never observed 2,6-*trans*-tetrahydropyran products from Prins cyclization reactions that would result from these higher energy intermediates.[22]

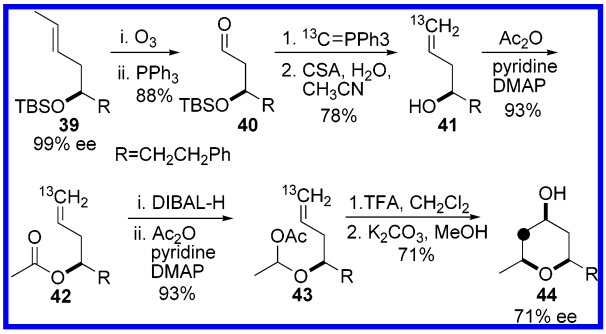


We were intrigued by the result shown in Table 2 (entry 3) in which Prins cyclization of acetoxy ether **32c** proceeded with complete retention of optical purity while cyclization of acetoxy ether **32a** showed a significant loss in optical purity. Could this surprising outcome be a result of different solvolysis behavior for terminal homoallylic systems versus substituted homoallylic systems? Solvolysis reactions of homoallylic systems with substituted alkenes have been shown at times to proceed with retention of stereochemistry.[19] We investigated this possibility with the reactions shown in eqs 2 and 3. Indeed, treatment of tosylate **35** with trifluoroacetic acid followed by methanolysis provided racemic alcohol **36**, whereas solvolysis of tosylate **37** led to optically pure alcohol **38**. Although this result correlates well with a solvolysis mechanism leading to racemization (Mechanism C or D), it does not provide definitive evidence. To unambiguously determine the mechanism for racemization in Prins cyclizations, we designed three isotopic labeling experiments to test the validity of the proposed mechanisms.



Acetoxy ether **43** containing a ^{13}C label at the terminal position of the alkene was designed to probe the validity of Mechanism C. The synthesis and Prins cyclization reaction of the isotopically labeled acetoxy ether **43** are shown in Scheme 1. Ozonolysis followed by reductive workup of optically active alkene **39** delivered aldehyde **40** in 88% yield. At this stage, a Wittig reaction installed the desired ^{13}C label and the silyl protecting group was removed to deliver homoallylic alcohol **41**. Esterification and reductive acetylation[21] then provided the desired acetoxy ether **43**. Prins cyclization and methanolysis[17] delivered tetrahydropyran **44** in 71% ee. Analysis of the ^{13}C NMR spectra clearly demonstrated that no scrambling of the ^{13}C label had occurred.

Scheme 1. Synthesis and Prins Cyclization of ^{13}C-Labeled Acetoxy Ether **43**

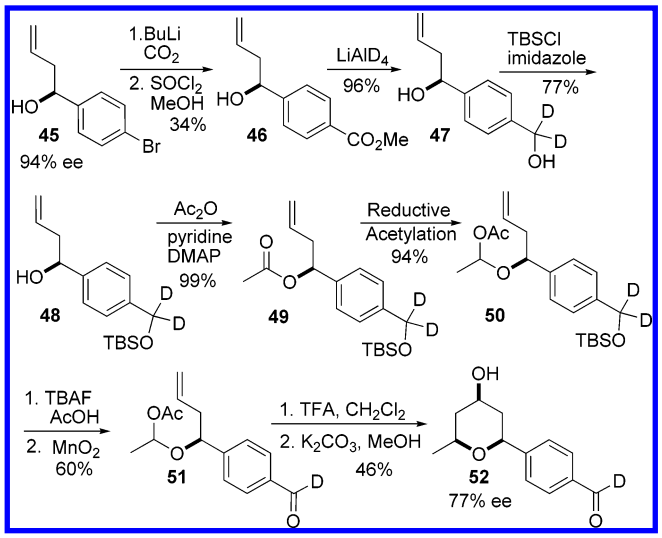


Deuterated acetoxy ether **51** was synthesized to investigate the role of Mechanism D. The synthesis began with optically active homoallylic alcohol **45** available from a Keck asymmetric allylation.[23] Carboxylation and esterification proceeded in

(22) (a) Trans products have been observed for vinylsilane-terminated cyclizations of ester-substituted oxocarbenium ion intermediates: Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426−3427. (b) Trans products have been observed when employing a substrate with a small sp-hybridized side chain: Hart, D. J.; Bennett, C. E. *Org. Lett.* **2003**, *5*, 1499−1502.

(23) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468.

Scheme 2. Synthesis and Prins Cyclization of Deuterated Acetoxy Ether **51**



moderate yield to deliver alcohol **46**. Treatment of alcohol **46** with lithium aluminum deuteride followed by selective primary alcohol protection led to deuterated alcohol **48**. Esterification and reductive acetylation[21] then provided acetoxy ether **50**. Silyl deprotection and benzylic oxidation completed the synthesis of the desired deuterated acetoxy ether **51**. Prins cyclization reaction then provided tetrahydropyran **52** in 46% yield and 77% ee (Scheme 2). In this case, we observed complete retention of deuteration at the aldehyde position.

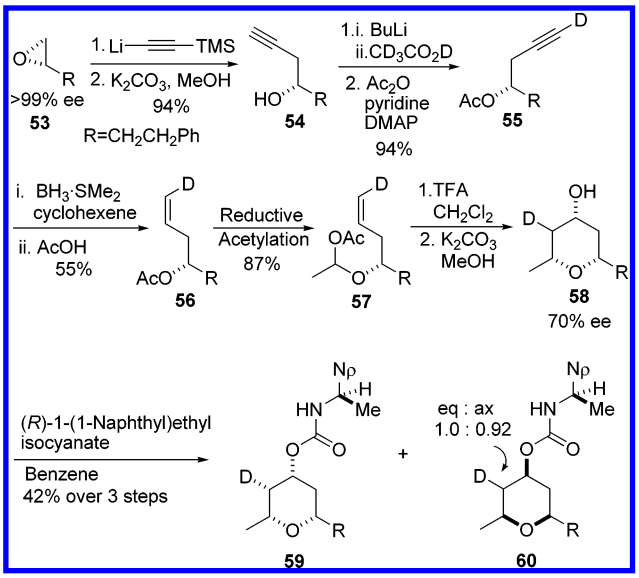
One additional isotopically labeled substrate was prepared to examine the potential role of Mechanism E in the loss of optical activity for Prins cyclization reactions. The synthesis of deuterated acetoxy ether **57** began with optically active epoxide **53** available from Jacobsen's hydrolytic kinetic resolution (Scheme 3).[24] Lithiated alkyne addition to the epoxide followed by deprotection provided alcohol **54** in 94% yield. The alkyne was then deprotonated with butyllithium and treated with deuterated acetic acid to install deuterium quantitatively at the terminal position of the alkyne. The alcohol was then esterified under standard conditions to provide compound **55**. Hydroboration followed by protonation led to ester **56**, which underwent reductive acetylation[21] smoothly to provide deuterated acetoxy ether **57**. Prins cyclization and methanolysis[17] then delivered tetrahydropyran **58** in 70% ee. At this point, we wished to determine the stereochemistry of the deuterium for each enantiomer. To facilitate this analysis, tetrahydropyran **58** was treated with an optically active chiral isocyanate[25] to generate diastereomeric tetrahydropyrans **59** and **60**. Tetrahydropyrans **59** and **60** were then carefully separated by preparatory HPLC and analyzed by deuterium NMR. The major isomer, tetrahydropyran **59**, had deuterium exclusively in the axial position, whereas the minor isomer, tetrahydropyran **60**, had deuterium located in both the equatorial and axial positions in a 1.0:0.92 ratio (Figure 8).

Discussion

Prins cyclization of the differentially labeled acetoxy ethers **43**, **51**, and **57** provides definitive evidence regarding the roles

(24) Schaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307−1315.
(25) Pirkle, W. H.; Boeder, C. W. *J. Org. Chem.* **1978**, *43*, 1950−1952.

Scheme 3. Synthesis and Prins Cyclization of Deuterated Acetoxy Ether **57**



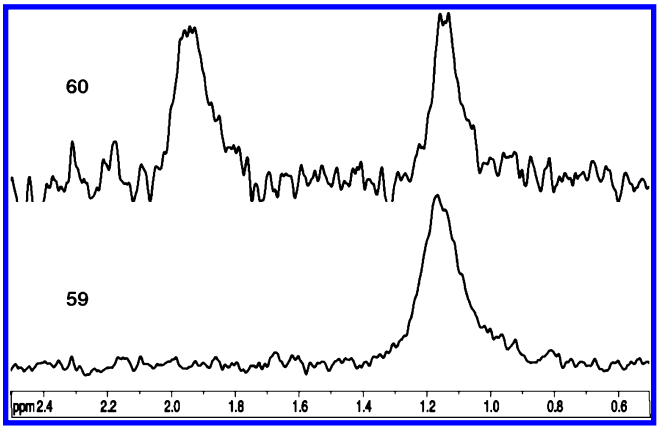


Figure 8. ^{2}H NMR spectra for tetrahydropyran **59** and tetrahydropyran **60**.

of Mechanisms C, D, and E for the loss of optical activity in Prins cyclization reactions. Prins cyclization of acetoxy ether **43**, in which no scrambling of the ^{13}C label was observed, can be used to rule out Mechanism C. Figure 9 illustrates the rationale for this conclusion. Treatment of acetoxy ether with trifluoroacetic acid generates oxocarbenium ion **61**. If oxocarbenium ion **61** continues on to tetrahydropyran **62**, the ^{13}C label will end up adjacent to the methyl side chain. However, if a fragmentation reaction occurs that eventually leads to intermediate cyclobutane **64**, the enantiomeric tetrahydropyran **67** will have the ^{13}C label adjacent to the R group instead of the methyl side chain. Analysis of the ^{13}C NMR spectra clearly revealed that the ^{13}C label had been completely retained in the position adjacent to the methyl group, therefore ruling out Mechanism C.

Having ruled out one fragmentation pathway, we turned our attention to Mechanism D. To probe Mechanism D, we utilized acetoxy ether **51** as an internal crossover probe that would take into account the possibility of solvent cage effects. Figure 10 illustrates this crossover experiment. Treatment of acetoxy ether **51** with trifluoroacetic acid initially generates oxocarbenium ion **68**. Oxocarbenium ion **68** can then lead to optically active

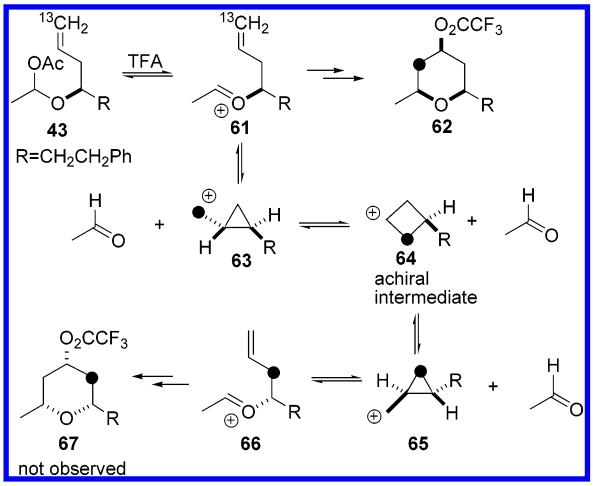


Figure 9. Loss of optical activity for Prins cyclizations is not due to Mechanism C.

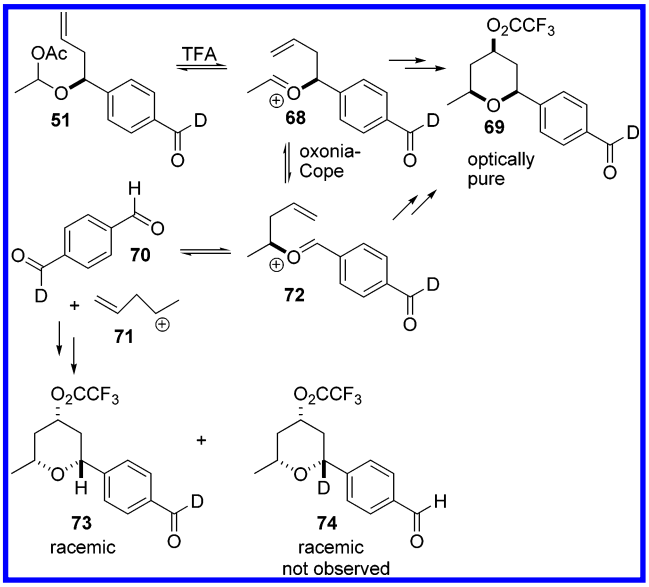


Figure 10. Loss of optical activity for Prins cyclizations is not due to Mechanism D.

tetrahydropyran **69**. Alternatively, a 2-oxonia-Cope rearrangement of oxocarbenium ion **68** should be rapid in this case to generate the more stable benzylic oxocarbenium ion **72**.[3e] Oxocarbenium ion **72** would lead to optically active tetrahydropyran **69**. If Mechanism D is operable, however, oxocarbenium ion **72** could also lead to fragmentation products **70** and **71**. Upon recombination, bis-aldehyde **70** could lead to either tetrahydropyran **73** or **74**. In contrast to the crossover experiment shown in eq 1, this more sensitive crossover experiment relies only on rotation of bis-aldehyde **70** occurring more rapidly than recombination with homoallylic cation **71**. Prins cyclization of acetoxy ether **51**, however, did not result in any observable amount of tetrahydropyran **74**. With this result in hand, we deemed Mechanism D extremely unlikely.

Prins cyclization of acetoxy ether **57** resulted in no deuterium scrambling for the major enantiomer but a 0.92:1.0 mixture of axial and equatorial deuterium for the minor enantiomer. This result clearly demonstrates that loss of optical activity in these Prins cyclization reactions occurs due to a 2-oxonia-Cope rearrangement by way of a (*Z*)-oxocarbenium (Mechanism E).[26] Rationale for this conclusion is depicted in the detailed mechanism shown in Figure 11. In this figure, we show 2-oxonia-Cope rearrangements and Prins cyclizations occurring through a common tetrahydropyranyl cation intermediate[9] to provide a complete mechanistic picture. Treatment of acetoxy ether **57** with trifluoroacetic acid initially generates oxocarbenium ion **75**. Oxocarbenium ion **75** can then cyclize to generate tetrahydropyranyl cation **76**, which upon nucleophilic trapping results in tetrahydropyran **77**. Alternatively, tetrahydropyranyl cation **76** could reopen to oxocarbenium ion **84**, which upon reclosure and nucleophilic trapping would also lead to tetrahydropyran **77**. Thus, both oxocarbenium ions **75** and **84** can lead to the major enantiomer, tetrahydropyran **77**, containing deuterium in an axial position. Loss in optical activity for these Prins cyclizations occurs when 2-oxonia-Cope rearrangements proceed through (*Z*)-oxocarbenium ion intermediates. For instance, (*E*)-oxocarbenium ion **75** could isomerize to (*Z*)-oxocarbenium ion **78**. Isomerization likely occurs by an addition−elimination pathway as opposed to higher energy mechanisms involving rotation or inversion.[11] This oxocarbenium ion can then lead to oxocarbenium ion **80** by way of a 2-oxonia-Cope rearrangement. Carbon−carbon bond rotation to place the methyl group in a pseudoequatorial position then leads to oxocarbenium ion **81**. Ring closure followed by nucleophilic trapping leads to the minor enantiomer, tetrahydropyran **83**. In this case, deuterium is incorporated into an equatorial position of the tetrahydropyran ring. Analogous to this enantiomerization pathway, oxocarbenium ion **84** can isomerize to oxocarbenium ion **85**, which then leads to tetrahydropyran **89**. For this pathway, however, tetrahydropyran **89** retains deuterium in an axial position in the tetrahydropyran ring. The 0.92 to 1.0 deuterium scrambling observed in the minor enantiomer is consistent with the lack of preference for formation of either oxocarbenium **78** or **85**. Interestingly, we did not observe *trans*-tetrahydropyrans resulting from nucleophilic trapping of either tetrahydropyranyl cation **79** or **86**.[27]

With a clearly defined mechanistic picture, the effects of reaction conditions (Table 1) can be further analyzed. The nucleophilicity of the anion is a key determinant in whether a loss in optical activity is observed for Prins cyclization reactions. Weak nucleophilic anions such as trifluoroacetate anion lead to a loss in optical activity (Table 1, entry 2), whereas stronger nucleophiles such as the tin-"ate" complex (Table 1, entry 7) preserve the optical activity of the starting material. This trend is easily rationalized from the fact that nucleophilic termination is a competing process to 2-oxonia-Cope rearrangements. More reactive nucleophiles, therefore, decrease the opportunity for unselective 2-oxonia-Cope rearrangements. The effects of temperature shown in Table 1 are also easily rationalized from Mechanism E. Higher temperatures (entry 1 versus entry 3) are necessary to access the higher energy intermediates such as cations **78**, **79**, and **80** that eventually lead to a loss in optical activity. Interestingly, solvent was also shown to play a crucial role in whether loss in optical activity is observed in these reactions (entry 2 versus entry 5). Prins cyclization promoted by trifluoroacetic acid in pentane resulted in complete retention of enantiomeric excess, whereas the same reaction performed

(26) Racemization by Mechanism D would not result in deuterium scrambling. The microscopic reverse of Mechanism E is also possible in which 2-oxonia-Cope rearrangement proceeds through the favorable *E*-oxocarbenium ion, but with the alkyl substituent in a pseudoaxial orientation.

(27) We did not isolate or observe the trans isomer by ^{1}H NMR. We cannot rule out the possibility that the trans isomer may be formed in very small quantity as a minor component.

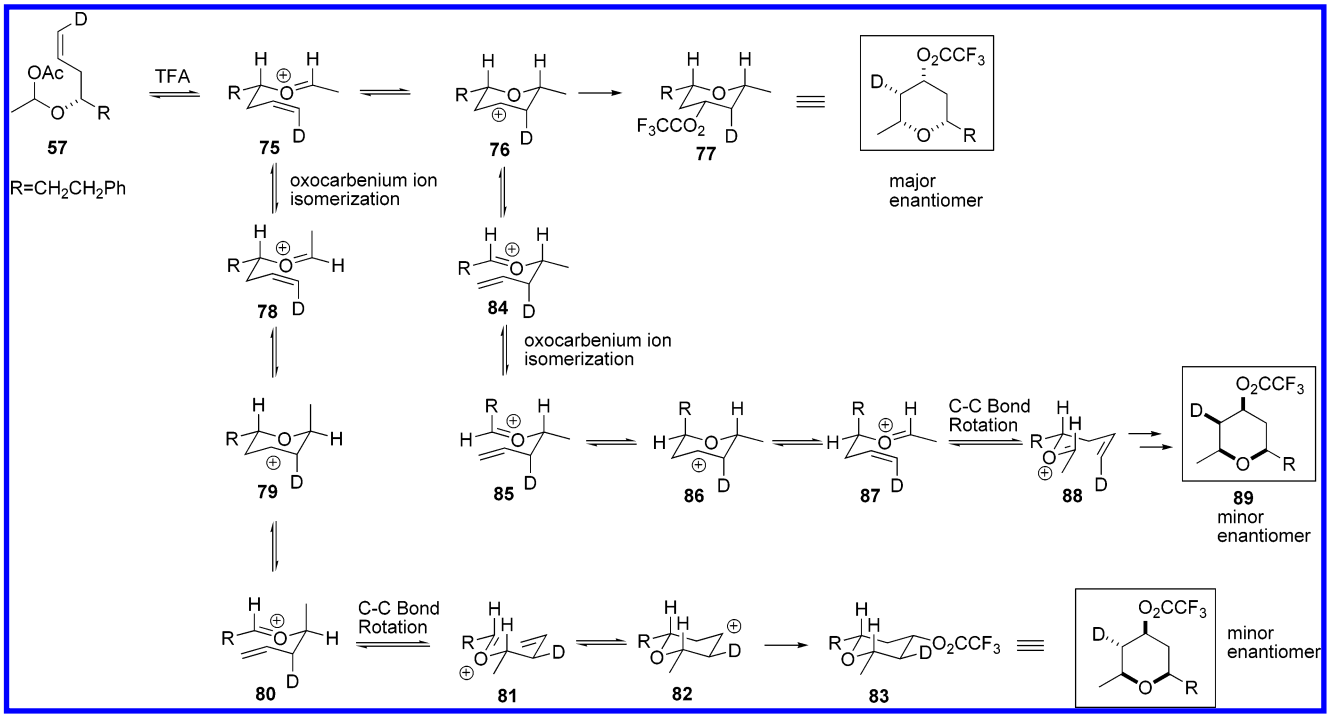


Figure 11. 2-Oxonia-Cope rearrangement through a (*Z*)-oxocarbenium ion leads to loss in optical activity for Prins cyclizations.

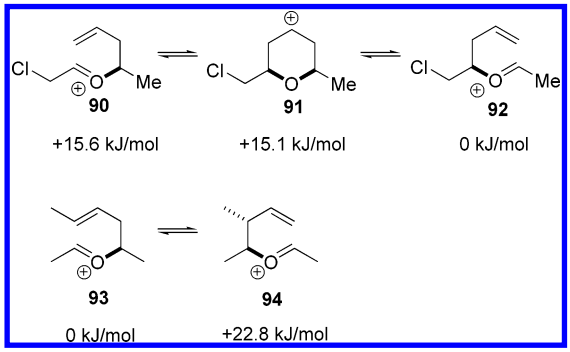


Figure 12. Structural features can reduce the rate of 2-oxonia-Cope rearrangement.

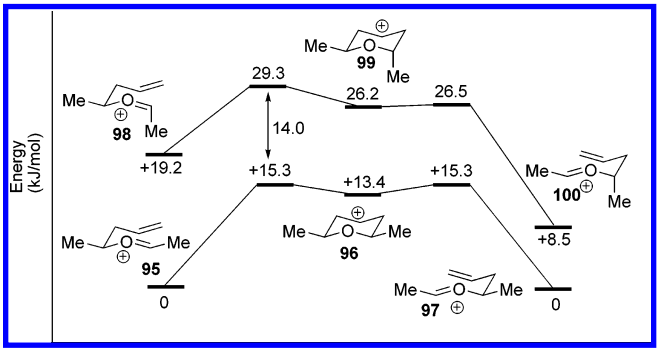


Figure 13. Energetics of enantiomerization.

in dichloromethane underwent partial racemization. In a nonpolar medium, the rate of nucleophilic addition to tetrahydropyranyl cation intermediate **76** (Figure 11) is expected to be greater due to decreased solvation of the nucleophile and the electrophile.[28]

The effects of structural features (Table 2) on the loss of optical activity for Prins cyclizations can also be rationalized from the mechanism shown in Figure 11. Racemization by Mechanism E relies on 2-oxonia-Cope rearrangements occurring many times before nucleophilic trapping. Only under these circumstances will the higher energy, less-populated (*Z*)-oxocarbenium ion intermediates have a noticeable influence on the optical activity of the tetrahydropyran products. Acetoxy ether **32b** incorporating a chloromethyl substituent does not satisfy these conditions. Treatment of acetoxy ether **32b** with trifluoroacetic acid will initially generate an oxocarbenium ion intermediate similar to **90** (Figure 12).[3e] This higher energy oxocarbenium ion will then rearrange via tetrahydropyranyl cation **91** to the more stable oxocarbenium ion **92**. Subsequent 2-oxonia-Cope rearrangement (**92** to **90**), however, will be slow due to the destabilizing effect of the chloromethyl group. This effect upon the rate of 2-oxonia-Cope rearrangement allows Prins cyclization of acetoxy ether **32b** to occur with no loss in optical activity. The same logic can be applied for Prins cyclization of (*E*)-alkene **32c**. In this case, 2-oxonia-Cope rearrangement of an (*E*)-alkene resulting in a terminal alkene should be slower than in the degenerate case (Table 2, entry 3 versus entry 1). In fact, oxocarbenium ion **94** is predicted to be 22.8 kJ/mol higher in energy than oxocarbenium ion **93**.[29,31] Additionally, one of the two possible pathways leading to racemization shown in Figure 11 (**78** to **83**) will lead to a diastereomer, not an enantiomer, in the case of a substituted alkene. A fast, reversible 2-oxonia-Cope rearrangement is required to allow the (*Z*)-oxocarbenium pathway to racemize the substrate.

Computational studies were performed to further investigate the pathway associated with Mechanism E. The energy diagram shown in Figure 13 demonstrates the different energetics

(28) See ref 3e for a similar effect.

(29) Geometry optimizations were performed with B3LYP/6-31G* as implemented in Gaussian 03 (ref 30). Minima were characterized by their vibrational frequencies.

(30) Frisch, M. J.; et al. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

(31) The unexpectedly large difference in energy between **93** and **94** can be attributed to more effective stabilization of the oxocarbenium ion in **93** by π-complex formation with the more highly substituted alkene.

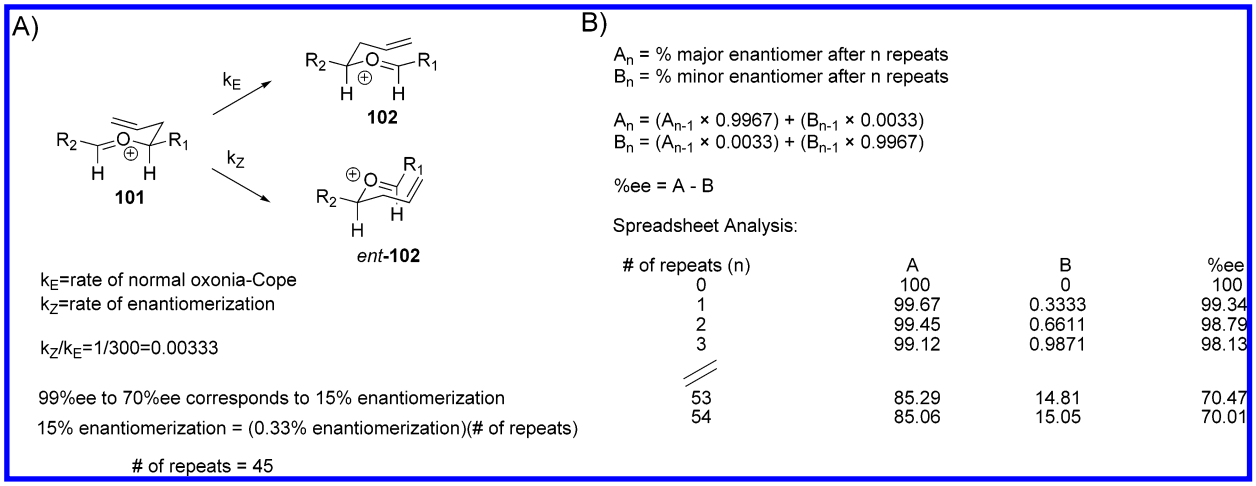


Figure 14. Oxonia-Cope rearrangement must occur many times for a significant loss in optical purity.

associated with the enantiomerization process (**98** to **100**) as opposed to the typical 2-oxonia-Cope rearrangement (**95** to **97**).[29] By utilizing the calculated energies, we can estimate relative rates of the enantiomerization process versus the rate of a standard 2-oxonia-Cope rearrangement. The highest activation barrier for the enantiomerization process is 14.0 kJ/mol greater than the highest activation barrier for the degenerate 2-oxonia-Cope rearrangement. This difference in activation energies translates to approximately a 300-fold difference in rates at room temperature. Therefore, we estimate that the normal 2-oxonia-Cope rearrangement occurs 300 times faster than the epimerizing 2-oxonia-Cope rearrangement.

With this calculated difference in rates, we can estimate the average number of 2-oxonia-Cope rearrangements required to result in the levels of racemization observed for these Prins cyclizations. This analysis is depicted in Figure 14a. The rate of the normal 2-oxonia-Cope rearrangement (**101** to **102**) is termed k_E, and the rate of the enantiomerization process (**101** to *ent*-**102**) is represented by k_Z. If every molecule on average underwent one oxonia-Cope rearrangement before nucleophilic trapping, approximately 0.33% of the material would be expected to proceed through the higher energy pathway and result in the enantiomeric tetrahydropyran. For the Prins cyclizaton shown in Scheme 3, acetoxy ether **57** (>99% ee) results in tetrahydropyran **58** in 70% ee. In other words, 15% of the material proceeded through the higher energy 2-oxonia-Cope rearrangement. If every 2-oxonia-Cope rearrangement results in 0.33% enantiomerization, on average every molecule must undergo approximately 45 2-oxonia-Cope rearrangements (45 repeats) before nucleophilic trapping to result in the observed loss in enantiomeric excess (Figure 14a). This simplified analysis does not take into account the fact that the epimerized material can correct itself through another 2-oxonia-Cope rearrangement by way of a (*Z*)-oxocarbenium ion. This process should be negligible at low levels of racemization but will become more significant as the amount of the minor enantiomer increases. When taking this back reaction into account (Figure 14b), a slightly greater number of repeats (54) are necessary for the level of racemization illustrated in Scheme 3.[32] This analysis highlights the fact that many 2-oxonia-Cope rearrangements must occur before nucleophilic trapping for Mechanism E to result in a significant loss in optical activity.

Conclusion

We have elucidated a pathway involving 2-oxonia-Cope rearrangements proceeding through (*Z*)-oxocarbenium ion intermediates that lead to a loss in optical purity for Prins cyclization reactions. These higher energy oxocarbenium ion intermediates become relevant when poor nucleophilic anions are used in the Prins cyclization reaction. By modifying reaction conditions such as solvent and temperature, this undesirable pathway can be minimized. In addition, structural features such as electron-withdrawing groups and alkene substitution can reduce the reversibility of the 2-oxonia-Cope rearrangement and, therefore, eliminate racemization in the Prins cyclization. These insights should be useful in expanding the scope and application of Prins cyclizations in synthesis.

Acknowledgment. This work was supported by the National Cancer Institute (CA081635) and by a generous gift from the Schering-Plough Research Institute. We thank Dr. Phil Dennison for assistance with NMR spectroscopy and Dr. John Greaves for mass spectrometry.

Supporting Information Available: Experimental details, complete ref 30, characterization of products, and coordinates for structures presented in Figures 12 and 13. This material is available free of charge via the Internet at http://pubs.acs.org.

JA064783L

(32) An expanded table for this calculation is provided in the Supporting Information.