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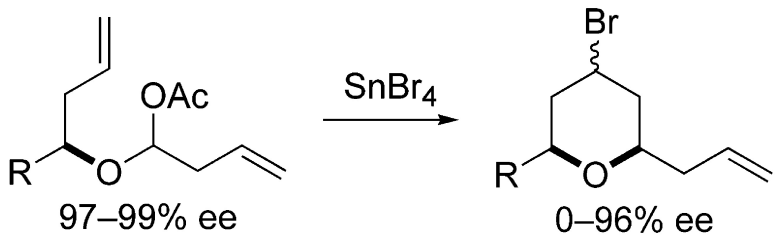

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Utilization of an Oxonia-Cope Rearrangement as a Mechanistic Probe for Prins Cyclizations

Ramesh Jasti, Christopher D. Anderson, and Scott D. Rychnovsky*

Contribution from the Department of Chemistry, University of California, Irvine, California 92697-2025

Received March 22, 2005; E-mail: srychnov@uci.edu

Abstract: An oxonia-Cope rearrangement was used as an internal clock reaction to probe the mechanism of the Prins cyclization reaction and the subsequent nucleophilic capture of the resultant tetrahydropyranyl cation. The oxonia-Cope rearrangement was shown to occur rapidly under typical Prins cyclization conditions when the oxocarbenium ion resulting from the rearrangement is similar to or lower in energy than the starting oxocarbenium ion. Oxonia-Cope rearrangements can be disfavored by destabilizing the resultant oxocarbenium ion or by stabilizing an intermediate tetrahydropyranyl cation. Stereoselectivity in the nucleophilic capture was dramatically affected by the reactivity of the nucleophile and electrophile. More reactive partners combined rapidly to give axial-substituted Prins products through a least-motion pathway. High selectivity for the equatorial-substituted tetrahydropyran was observed for less reactive nucleophiles and electrophiles.

Introduction

The Prins cyclization is a powerful transformation to generate highly substituted tetrahydropyrans with excellent stereoselectivity.[1,2] Many variations of this transformation have been investigated and continue to be explored. Although this cyclization has garnered significant attention from the chemical community, the following two mechanistic aspects of this transformation are not well understood: (1) the relative rates of Prins cyclization versus a competing oxonia-Cope rearrangement, and (2) the stereoselectivity of nucleophilic capture of the resulting cation following cyclization (Figure 1).

Several authors have reported the oxonia-Cope rearrangement as a competitive process in Prins cyclizations and related transformations.[3,4] Although similar reactions such as Claisen and Cope rearrangements typically require heating,[5] oxonia-Cope rearrangements proceed rapidly at temperatures as low as −78 °C. In fact, we have recently demonstrated a tandem reaction in which an initial oxonia-Cope rearrangement is followed by Prins cyclization to generate tetrahydropyranones with quaternary centers (Figure 2).[6] Inherent in the further development and utilization of tandem reactions of this nature is the need to have a general understanding of the rates of oxonia-Cope rearrangements versus Prins cyclizations.

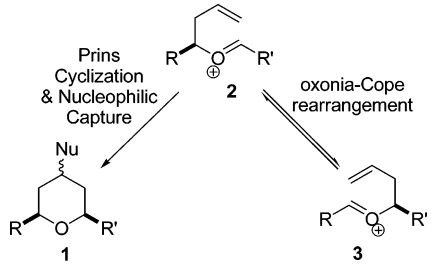

Figure 1. Prins cyclization and oxonia-Cope rearrangement.

Prins cyclizations are typically highly selective for the all-cis tetrahydropyran. A rationale for the all-cis stereoselectivity has been set forth by computational work from Alder (Figure 3A).[7] Alder suggests that initial Prins cyclization of an (*E*)-oxocarbenium ion[8] through a chair-like transition state leads to tetrahydropyranyl cation **7**. Tetrahydropyranyl cation **7** has

(1) For reviews on the Prins cyclization, see: (a) Arundale, E.; Mikeska, L. A. *Chem. Rev.* **1952**, *52*, 505−555. (b) Adams, D. R.; Bhatnagar, S. P. *Synthesis* **1977**, 661−672. (c) Snider, B. B. In *The Prins Reaction and Carbonyl Ene Reactions*; Trost, B. M., Fleming, I., Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, pp 527−561. (d) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143−7157.

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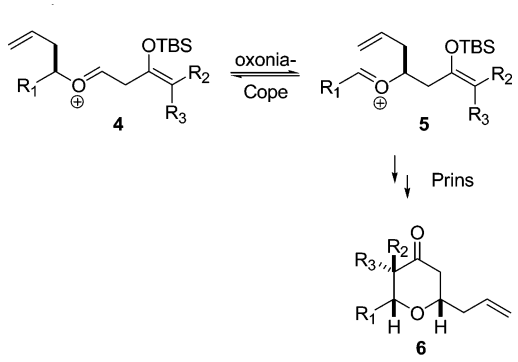
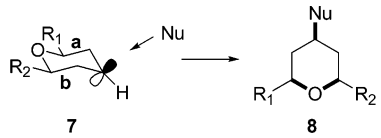
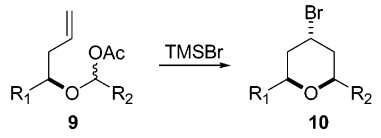


Figure 2. Oxonia-Cope Prins cyclization.



A. Alder Model to Explain Equatorial Stereoselectivity



B. Axial-Selective Prins Cyclization

Figure 3. Diastereoselectivity of Prins cyclizations.

increased stabilility due to delocalization. Bonds **a** and **b** and the lone pair on oxygen are in alignment with the empty p orbital, creating a six-electron system in the equatorial plane of the ring. The optimal geometry for delocalization places the hydrogen at C4 in a pseudoaxial geometry, thereby favoring nucleophilic trapping from an equatorial trajectory. Recently, we have reported Prins cyclizations that are not consistent with this rationale. Acetoxy ethers, upon treatment with bromotrimethylsilane (TMSBr), cyclize to produce 2,6-*cis*-4-*trans* tetrahydropyrans (Figure 3B).[9] We have proposed a least-motion pathway[10] from an intimate ion pair[11] to explain the unusual axial-selective Prins cyclization, but further experiments are warranted to fully validate this hypothesis.

In this article, we describe experiments designed to investigate the relative rates of oxonia-Cope rearrangement versus Prins cyclization and the stereoselectivity of nucleophilic attack at C4. We provide evidence that the oxonia-Cope rearrangement is a rapid process relative to Prins cyclization under most reaction conditions. We also demonstrate that certain structural elements and reaction conditions alter the relative rates of Prins cyclization versus oxonia-Cope rearrangement. In addition, we show that these same structural elements and reaction conditions also can have a dramatic effect upon the stereoselectivity of nucleophilic capture.

Experimental Design

In general, oxonia-Cope rearrangements occur rapidly and cannot be detected by product analysis. Figure 4 outlines a test that we previously used to demonstrate fast oxonia-Cope rearrangements in a Prins cyclization substrate.[12] Upon treatment with Lewis acid, acetoxy ether **11** generates oxocarbenium ion **12**. This oxocarbenium ion can undergo rearrangement to oxocarbenium ion **13** via an oxonia-Cope pathway. Either oxocarbenium ion **12** or **13** will lead to the same Prins cyclization product **14**. However, direct hydride addition to oxocarbenium ion **12** produces (*R*)-**15**, whereas direct hydride addition to oxocarbenium ion **13** produces (*S*)-**15**. When acetoxy ether **16** was treated with $BF_3{\cdot}OEt_2$ in the presence of triethylsilane, ether **17** was isolated in 3.5% enantiomeric excess. The significant loss in optical activity demonstrates that oxonia-Cope rearrangement is a fast process under these reaction conditions. Although this experiment suggests that the oxonia-Cope rearrangement occurs at a faster rate than Prins cyclization, it does not provide direct evidence to support this conclusion. In this experiment, the oxonia-Cope rearrangement is shown to be faster than [1,2]-hydride addition to an oxocarbenium ion. A more exact experiment was needed to determine the relative rates of oxonia-Cope rearrangement versus Prins cyclization.

Figure 5 outlines a test that would allow for the direct comparison of the rate of oxonia-Cope rearrangement versus the rate of Prins cyclization. In this case, treating acetoxy ether **18** with a Lewis acid would generate oxocarbenium ion **19**. In light of Alder's model, **19** should cyclize to provide tetrahydropyranyl cation intermediate **20**. Alder suggests this cation is an intermediate for both Prins cyclizations and oxonia-Cope rearrangements.[7] This argument is supported by the often simultaneous occurrence of the two processes and the evidence of charged intermediates in similar rearrangements.[13] Therefore, we shall illustrate tetrahydropyranyl cation **20** as a branch point in the mechanism of an oxonia-Cope rearrangement and Prins cyclization. However, we cannot rule out a concerted pathway for oxonia-Cope rearrangment. Direct nucleophilic trapping of tetrahydropyranyl cation **20** would lead to optically active tetrahydropyran **21**. Tetrahydropyranyl cation **20** could also undergo a ring-opening process that leads to either initial oxocarbenium ion **19** or achiral oxocarbenium ion **22**. The achiral oxocarbenium ion **22** necessarily leads to racemic tetrahydropyran **21**. Thus, the oxonia-Cope rearrangement mediates racemization. Unlike the test presented in Figure 4, this test would allow for the cyclization of several acetoxy ethers under a variety of conditions that lead to Prins cyclization. Measuring the enantiomeric excess of the product tetrahydropyrans would then allow us to directly compare the rates of the oxonia-Cope rearrangement (**19** to **22**) versus the Prins cyclization reaction (**19** to **21**). The enantiomeric excess would reflect the difference in rates of ring-opening (**20** to **22**) versus the rate of nucleophilic capture (**20** to **21**). In addition, we hoped that analysis of enantiomeric excess of axial-selective Prins cyclizations would shed light on our hypothesized least-motion pathway mechanism.[9]

Synthesis of Substrates

Acetoxy ethers were prepared by standard means developed in our laboratory.[14] Scheme 1 outlines the synthesis of acetoxy ether **25**. Asymmetric allylation of hydrocinnamaldehyde provided optically active alcohol **23** in 97% ee.[15] Alcohol **23** was then coupled to vinyl acetic acid in 93% yield. Reductive acetylation of ester **24** then provided acetoxy ether **25** in 97% yield.[14] Other acetoxy ethers used in this study were synthesized in similar fashion, and further details are provided in the Supporting Information.

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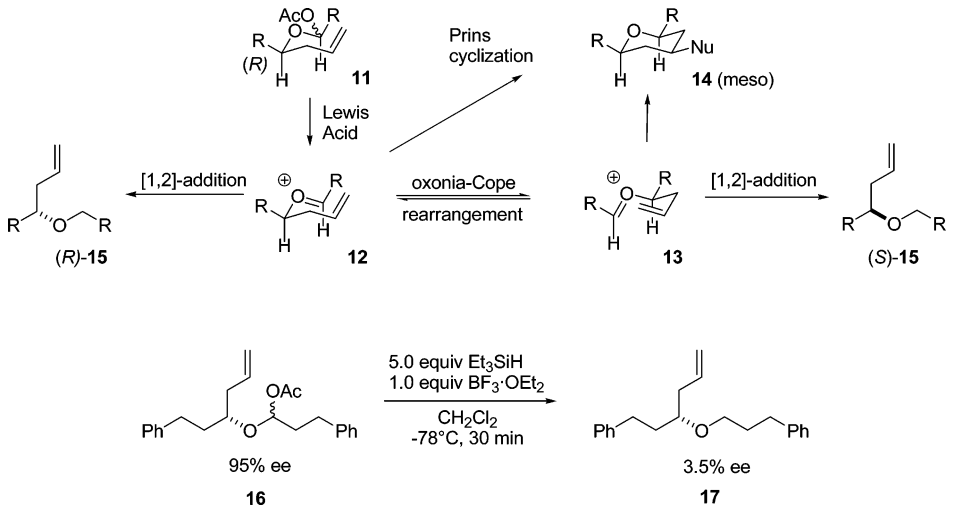


Figure 4. Test for comparison of rate of oxonia-Cope rearrangement vs rate of [1,2]-hydride addition.

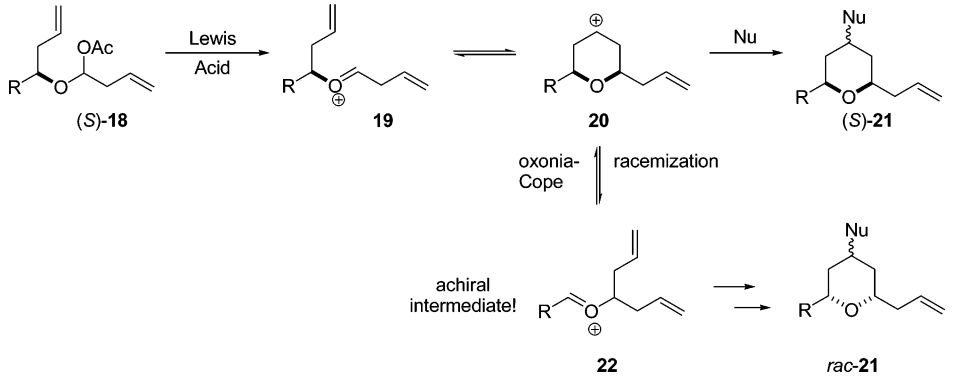
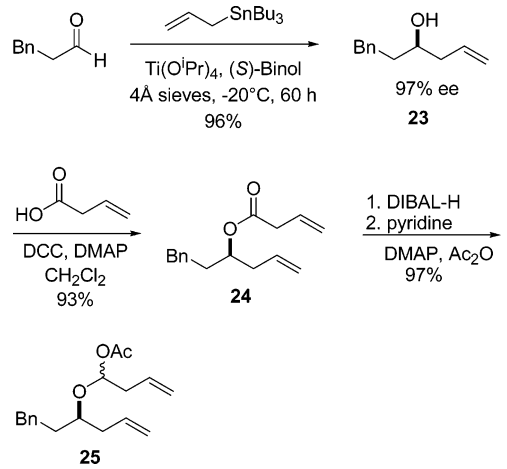


Figure 5. Test for direct comparison of rate of oxonia-Cope rearrangement vs rate of Prins cyclization.

Scheme 1. Synthesis of Optically Active Acetoxy Ether **25**



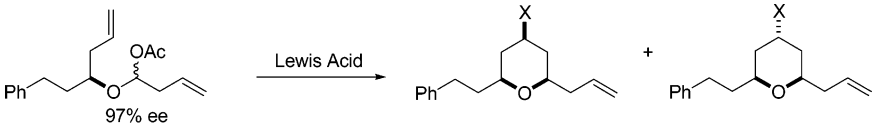
Results

Our initial experiments focused on a variety of Prins cyclization conditions for acetoxy ether **25** (Table 1). Cyclization of acetoxy ether **25** with $SnBr_4$ led to tetrahydropyrans **26** and **27** in a 1.8:1.0 ratio. Both diastereomers were shown to have low levels of optical activity, 8% ee for **26** and 9% ee for **27**. The similar enantiomeric excess for both diastereomeric tetrahydropyrans is consistent with Alder's suggestion of a tetrahydropyranyl cation intermediate. Comparison of entries 1 and 2 demonstrates the lack of temperature dependence on the relative rates of Prins cyclization versus oxonia-Cope rearrangement. Entries 2, 3, and 4 suggest a significant solvent dependence on relative rates of the two processes. A nonpolar solvent such as hexanes led to higher levels of optical activity, whereas a more polar solvent such as nitromethane produced racemic products. Interestingly, polar solvent also led to higher selectivity for the equatorial trapped tetrahydropyran **26**. As expected, our recently reported TMSBr conditions produced axial-substituted tetrahydropyran **27**. The TMSBr-initiated Prins cyclization was the only reaction condition that led to tetrahydropyran products with high levels of enantiomeric excess (79% ee).

With an initial survey of reaction conditions completed, our attention turned to the effects of nucleophile concentration (Table 2). We chose entry 1 in Table 1 as our standard reaction conditions in which we would vary nucleophile concentration. For the $SnBr_4$-mediated cyclizations, the active nucleophile is a tin-"ate" complex generated upon solvolysis of the acetoxy ether. Tetrabutylammonium bromide was premixed with $SnBr_4$ in order to generate a similar tin-"ate" complex that could serve as a source of nucleophilic bromide. This additive could then easily be prepared in different concentrations and utilized in our concentration experiments. The data in Table 2 demonstrates that the relative rates of oxonia-Cope versus Prins cyclization are only minimally affected by nucleophile concentration.

We chose acetoxy ether **25** as our initial substrate in order to analyze reaction conditions in a system that would not energetically favor either initial oxocarbenium ion **19** or achiral oxocarbenium ion **22**. We predicted that electron-withdrawing

Table 1. Effect of Reaction Conditions on Rate of Oxonia-Cope vs Prins Cyclization

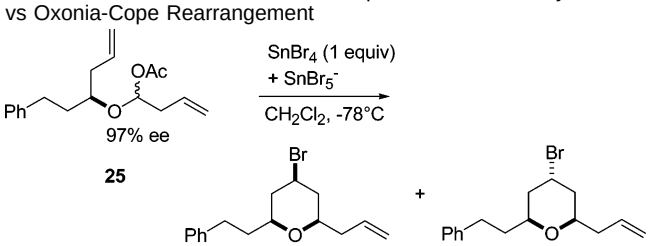


25 **26** **27**

entry	Lewis acid	X	solvent	temp (°C)	yield[a] (%)	**26**:**27**[b]	ee **26**[c] (%)	ee **27**[c] (%)
1	$SnBr_4$	−Br	CH_2Cl_2	−78	93	1.8:1.0	8	9
2	$SnBr_4$	−Br	CH_2Cl_2	0	90	3.0:1.0	9	10
3	$SnBr_4$	−Br	hexanes	0	64	3.1:1.0	31	36
4	$SnBr_4$	−Br	$MeNO_2$	0	82	11:1.0	0	0
5	$SnCl_4$	−Cl	CH_2Cl_2	0	81	3.7:1.0	7	8
6	TMSBr	−Br	CH_2Cl_2	0	85	1.0:14		79
7	$BF_3{\cdot}OEt_2$	$-O_2CCH_3$	hexanes	0	52	>19:1.0	13	
8	TFA	$-O_2CCF_3$[d]	CH_2Cl_2	0	92	>19:1.0	5	

[a] Yield of product after flash chromatography. [b] Diastereoselectivity determined by ^{1}H NMR analysis of crude material. [c] Enantioselectivity determined by HPLC using a Chiracel OD-H column. Authentic racemates were synthesized by cyclization of racemic acetoxy ether. [d] Analysis was conducted after hydrolysis of the trifluoroacetate with K_2CO_3/MeOH.

Table 2. Effect of Bromide Additive upon Rate of Prins Cyclization vs Oxonia-Cope Rearrangement

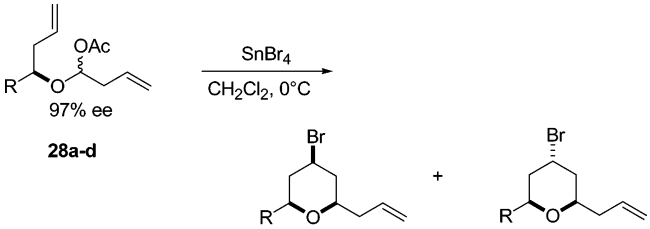


25 **26** **27**

entry	$[SnBr_5^-]$[a] (M)	yield[b] (%)	**26**:**27**[c]	ee **26**[d] (%)	ee **27**[d] (%)
1	0.05	56	1.8:1.0	13	13
2	0.25	59	2.4:1.0	16	17
3	0.50	59	2.7:1.0	18	19

[a] Tin-"ate" complex was prepared by premixing $SnBr_4$ and $Bu_4N^+Br^-$ in a 1:1 ratio. [b] Yield of product after flash chromatography. [c] Diastereoselectivity determined by ^{1}H NMR analysis of crude material. [d] Enantioselectivity determined by HPLC using a Chiracel OD-H column.

Table 3. Substituent Effects on Rate of Prins Cyclization vs Oxonia-Cope Rearrangement



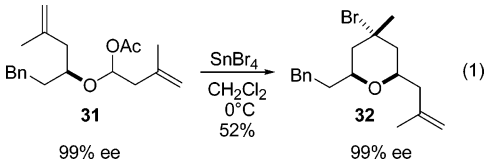
28a-d

			29a-d			**30a-d**	
entry	starting material	R group	ee **28**[a] (%)	yield[b] (%)	**29**:**30**[c]	ee **29**[d] (%)	ee **30**[d] (%)
1	**28a**	$PhCH_2CH_2-$	97	80	3.0:1.0	9	10
2	**28b**	CH_2CH-	92	66	19:1.0	0	n/a
3	**28c**	$TBDPSOCH_2-$	98	69	1.0:1.5	57	56
4	**28d**	$ClCH_2-$	99	55	1.0:4.0	96	96

[a] Enantiomeric excess for acetoxy ethers was established from starting homoallylic alcohols. Alcohols were assayed by either chiral HPLC or GC analysis. [b] Yield of product after flash chromatography. [c] Diastereoselectivity determined by ^{1}H NMR analysis of crude material. [d] Enantioselectivity determined by either chiral HPLC or GC analysis.

groups or stabilizing groups could have a significant influence on the relative rates of the oxonia-Cope rearrangement versus Prins cyclization. Table 3 highlights these results. Entry 2 demonstrated that stabilizing oxocarbenium ion **22** with a vinyl substituent leads to total loss of optical purity. Interestingly, in this case the Prins reaction was highly selective for the equatorial-substituted product. Introduction of an electron-withdrawing group (entry 3) led to higher levels of optical activity and 1.0 to 1.5 selectivity in favor of the axial bromide product. Introducing an even more powerful electron-withdrawing group to destabilize achiral oxocarbenium ion **22** (entry 4) resulted in a 4.0 to 1.0 axial-selective Prins cyclization with virtually no loss of enantiomeric excess.

Having probed stabilizing and destabilizing electronic effects upon oxocarbenium ion **19**, we turned our attention to tetrahydropyranyl cation **20**. Stabilizing the tetrahydropyranyl cation intermediate with a third alkyl group could have significant effects upon the rates of oxonia-Cope versus Prins cyclization. To explore this concept, acetoxy ether **31** was synthesized. Cyclization of acetoxy ether **31** with $SnBr_4$ generated the axial bromide tetrahydropyran **32** with no erosion of enantiomeric excess (eq 1).



31 99% ee **32** 99% ee

Discussion

Table 1 definitively shows that oxonia-Cope rearrangement is a rapid process relative to Prins cyclization under standard Prins cyclization conditions. Interestingly, conditions employing TMSBr as a Lewis acid (Table 1, entry 6) were the only conditions that led to tetrahydropyran with moderate levels of optical activity. A rationale for this result is presented in Figure 6. Treatment of an acetoxy ether with $SnBr_4$ generates oxocarbenium ion **34** and a tin-"ate" complex. Cyclization results in a higher energy tetrahydropyranyl cation **35**.[7] This intermediate can then undergo either of two ring-opening process to generate intermediates **34** or **36**. Intermediate **36** will result in racemic tetrahydropyran product. However, if **35** is attacked by bromide before ring-opening can occur, **37** should be isolated with

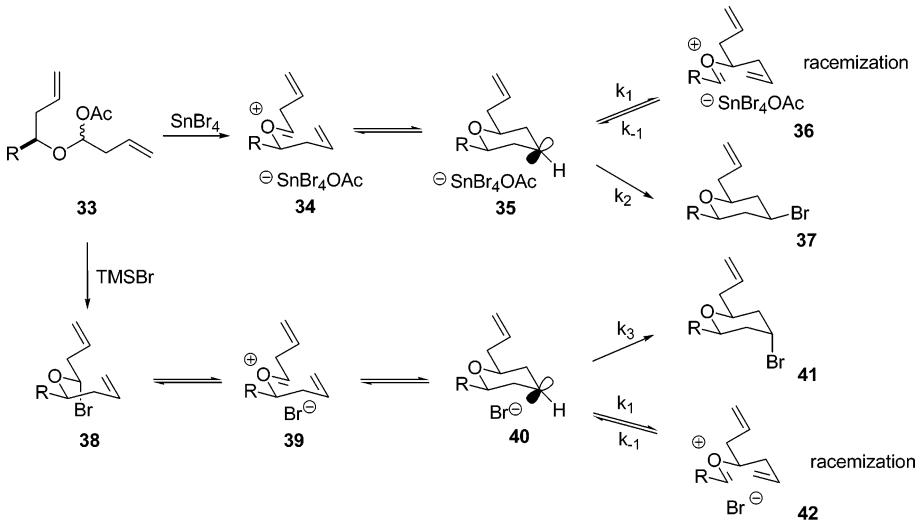


Figure 6. Comparison of $SnBr_4$ and bromotrimethylsilane-initiated Prins cyclizations.

enantiomeric excess identical to that of starting acetoxy ether **33**. The significant racemization shown in Table 1 suggests that k_1 is typically greater than k_2. Treatment of acetoxy ether **33** with TMSBr, however, generates bromoether **38**, which can then solvolyze to oxocarbenium ion **39**.[9] In this case, the nucleophile generated is bromide, which should be much more reactive than a tin-"ate" complex. As expected, k_3 is greater than k_1, and tetrahydropyranyl cation **40** is trapped to generate axial tetrahydropyran **41** with moderate levels of enantiomeric excess.

The argument presented in Figure 6 would seem to imply that nucleophile concentration should have an effect on the rates of oxonia-Cope versus Prins cyclization. The results in Table 2, however, show that this is not the case. A 10-fold increase in concentration of nucleophile only minimally affected the enantiomeric excess of products. This can perhaps be explained by the role of ion-pairing.[16] Oxocarbenium ions such as **34** and **39** may exist as ion-pairs, retaining close proximity to a counterion. This counterion also serves as a nucleophile. Therefore, if internal return of a nucleophile (inside a solvent cage) is fast relative to incorporation of an external nucleophile (outside a solvent cage), nucleophile concentration would have minimal effect. This hypothesis also seems to be consistent with the solvent effects shown in Table 1, entries 3 and 4. A less polar solvent such as hexanes should favor ion-pairing, thus leading to higher levels of optical activity. In contrast, nitromethane should disfavor ion-pairing and lead to more racemization. Crossover experiments would be useful in a further investigation of ion-pairing effects in Prins cyclizations.[17]

Figure 6 can also be used to analyze results presented in Table 3. An acetoxy ether possessing an electron-withdrawing group such as a chloromethyl substituent (Table 3, entry 4) destabilizes oxocarbenium ion **36**. In this case, the rate of ring-opening to **36** is slower than nucleophilic attack by bromide. Consistent with this explanation, tetrahydropyran **30d** was isolated in 96% ee. Replacing the electron-withdrawing group with a vinyl group had the opposite effect. The vinyl group stabilizes oxocarbenium ion **36** and is reflected in the transition state from **35** to **36**. For the vinyl-substituted acetoxy ether **28b**, k_1 is greater than k_2 and racemic product **29b** is isolated.

Stabilizing and destabilizing groups also had an effect on the diastereoselectivity of the Prins cyclization. Electron-withdrawing groups such as chloride and oxygen (Table 3, entries 3 and 4) lessen the extent of delocalization of tetrahydropyranyl cation intermediate **35**. The more reactive cation leads to more of the axial product. This effect can be rationalized in a fashion similar to the argument presented for trimethylsilyl bromide-initiated cyclizations.[9] Cyclizations utilizing TMSBr generate a very reactive nucleophile, bromide. Bromide, because of its high reactivity, tends to react through a least-motion pathway,[10] leading to axial trapped product. The diastereoselectivity of the reaction seems to be controlled by the probability of collision as opposed to differences in energy of transition states.[18] In other words, approach from an equatorial trajectory should lead to a lower transition state energy; however, collision from an axial trajectory may have a greater probability of occurrence. In the case of a very reactive nucleophile, most collisions may lead to product, and differences in transition state energies would have minimal effect on the diastereoselectivity. Similar to the case for very reactive nucleophiles, more reactive electrophiles should be trapped through a least-motion pathway (**28d** leads to high axial selectivity). In contrast, the vinyl-substituted acetoxy ether **28b** generates a less reactive electrophile, and stereoselectivity should reflect the differences in transition state energies. Consistent with this reasoning, **28b** produced equatorial-substituted tetrahydropyran **29b** in high selectivity.

To provide further insight into the observed electronic effects, DFT calculations were performed.[19] The results of these calculations are summarized in the energy diagrams shown in Figure 7. Alder has shown that *cis*-2,6-dimethyl-4-tetrahydro-

(16) Sneen, R. A. *Acc. Chem. Res.* **1973**, *6*, 46−53.
(17) A reviewer suggested a crossover experiment utilizing tetrabutylammonium chloride as a competitive nucleophile. We found that generation of a bromoether from acetoxy ether **25** at −60 °C followed by addition of tetrabutylammonium chloride and warming to 0 °C led to axial bromotetrahydropyran **27** in 83% ee. No chlorotetrahydropyrans were observed in the crude reaction mixture. This result is consistent with an ion-pairing argument in which recombination of a bromide anion from inside a solvent cage is faster than incorporation of a chloride anion from outside a solvent cage.
(18) Carbocations which are not highly stabilized are known to be quenched at a diffusional rate: (a) McCelland, R. A. *Tetrahedron* **1996**, *52*, 6823. (b) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981−988.
(19) Geometry optimizations were performed with B3LYP/6-31G* as implemented in Gaussian 03.[20] Minima were characterized by their vibrational frequencies. Reported energies include unscaled zero-point corrections.
(20) Frisch, M. J.; et al. *Gaussian 03*, Revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

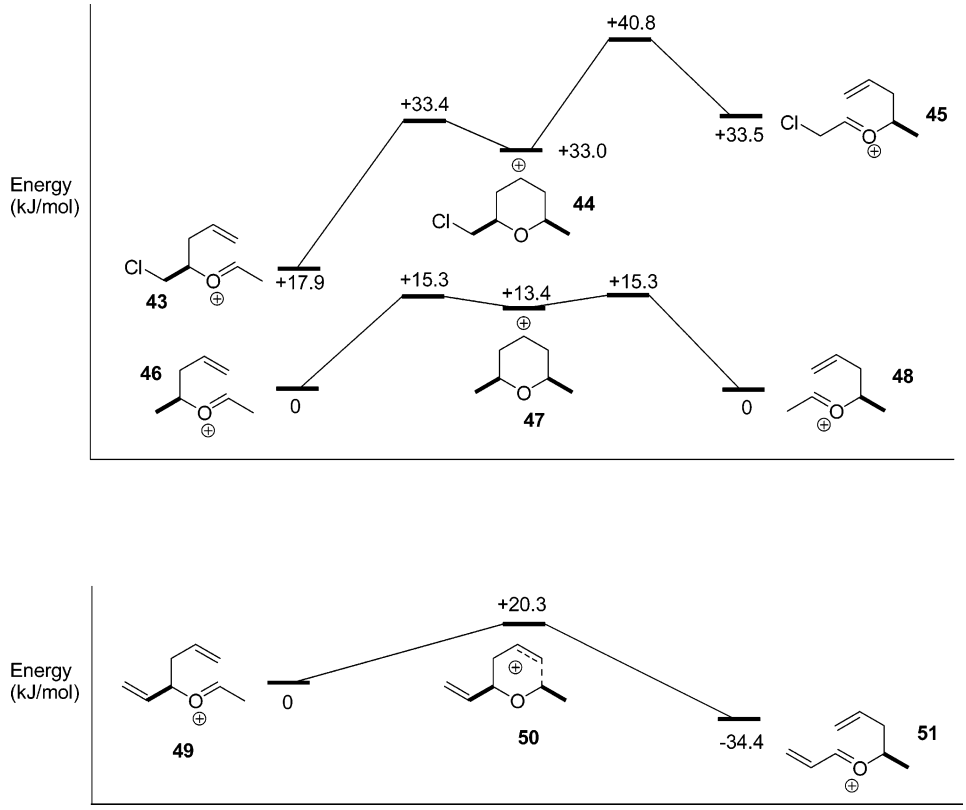
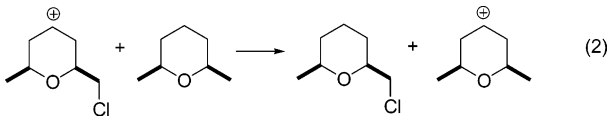
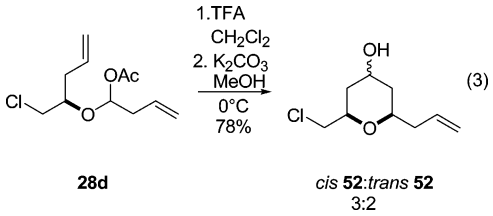


Figure 7. Substituent effects on energy profile of oxonia-Cope rearrangement.

pyranyl cation **47** is 13.4 kJ/mol less stable than its open form and is protected from ring-opening by an activation energy of 1.9 kJ/mol. The incorporation of a chloromethyl substituent results in a significant increase in activation energy of ring-opening to oxocarbenium ion **45**. Ring-opening from tetrahydropyranyl cation **44** to oxocarbenium ion **45** requires an activation energy of 7.8 kJ/mol, whereas ring-opening from **44** to **43** requires only 0.4 kJ/mol. This energy profile correlates well with the high optical activity observed for the cyclization of acetoxy ether **28d** (Table 3). In addition, the isodesmic reaction in eq 2 shows that the chloride-substituted tetrahydropyranyl cation **44** is 19.6 kJ/mol higher in energy than cation **47**. This destabilization is consistent with our hypothesis of more reactive electrophiles leading to axial-selective Prins cyclizations through a least-motion pathway. A more comprehensive set of examples would be necessary to further validate this hypothesis. Interestingly, we were not able to locate a tetrahydropyranyl cation intermediate for the vinyl-substituted oxocarbenium ion **49**, perhaps indicating a concerted pathway.



Equation 3 shows an additional experiment to further investigate the least-motion pathway argument presented above. We rationalized that cyclization of acetoxy **28d** in the presence of a less reactive nucleophile should lead to more of the equatorial-substituted product. Indeed, treatment of acetoxy ether **28d** with trifuoroacetic acid followed by hydrolysis of the trifloroacetate produced tetrahydropyrans **52** in a 3:2 ratio favoring the all-cis tetrahydropyran.



Cyclization of acetoxy ether **31** produced tetrahydropyran **32** with no loss of optical activity. This result is consistent with tetrahydropyranyl cation stabilization. Lowering of the energy of the tetrahydropyranyl cation intermediate effectively raises the transition state energy for ring-opening to the achiral oxocarbenium ion. Computational work supports this hypothesis (Figure 8). Alder has shown that tetrahydropyranyl cation **47** is 13.4 kJ/mol less stable than oxocarbenium ion **46**.[7] Ring-opening of cation **47** to oxocarbenium ion **46** is protected by an activation barrier of only 1.9 kJ/mol. These results are consistent with rapid oxonia-Cope rearrangements for mono-substituted olefins. In contrast, oxocarbenium ion **53** is 40.9 kJ/mol higher in energy than tetrahydropyranyl cation **54**.[19]

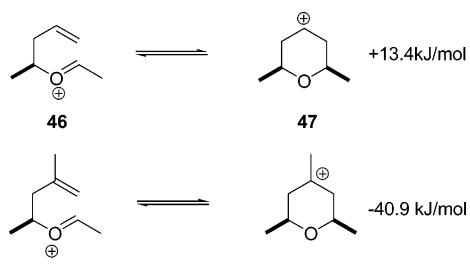


Figure 8. Stabilization of tetrahydropyranyl cation.

Thus, acetoxy ether **31** cyclizes to tetrahydropyran **32** with no loss of optical activity. In this case, cyclization is essentially irreversible (ring-opening does not occur before nucleophilic capture).

Conclusion

These results utilizing an oxonia-Cope rearrangement as an internal clock reaction provide useful mechanistic insight into the Prins cyclization. For a typical Prins cyclization substrate, oxonia-Cope is fast relative to nucleophilic capture of an intermediate tetrahydropyranyl cation. By stabilizing or destabilizing the resultant oxocarbenium ion, the oxonia-Cope rearrangement can be accelerated or decelerated. In addition, stabilizing the tetrahydropyranyl cation intermediate raises the transition state energy for ring-opening and effectively eliminates oxonia-Cope rearrangement. Stereoselectivity of nucleophilic capture at C4 is highly dependent on the reactivity of the nucleophile and electrophile. Highly reactive nucleophiles and electrophiles provide axial-substituted tetrahydropyrans, whereas less reactive nucleophiles and electrophiles provide equatorial-substituted tetrahydropyrans.

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Supporting Information Available: Complete experimental details, complete ref 20, characterization of products, and coordinates for structures presented in Figures 7 and 8. This material is available free of charge via the Internet at http://pubs.acs.org.

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