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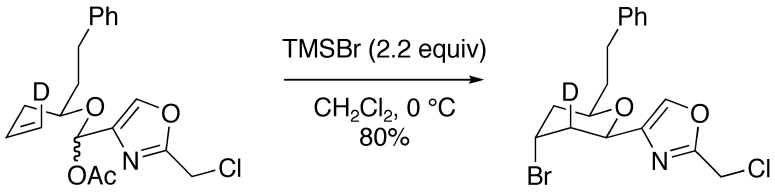

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Axial-Selective Prins Cyclizations by Solvolysis of α-Bromo Ethers

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The electrophilic cyclization of homoallylic ethers with aldehydes under strongly acidic conditions was explored by Hanschke[1] and later by Stapp[2] and came to be known as the Prins cyclization.[3,4] The reaction leads to formation of a tetrahydropyran with a heteroatom at the 4-position, and virtually all cases proceed with modest to high selectivity for the equatorial product at the 4-position.[5] Alder's recent computational analysis identified a delocalized cationic intermediate in the cyclization that would favor equatorial addition of a heteroatom by orbital alignment.[6] We now report an experimental modification of our segment-coupling strategy[7] that selectively generates the 4-axial products in Prins cyclizations.

The project originated in a synthetic approach to phorboxazole and was stimulated by the difficulty we encountered in the cyclization of a variety of substrates containing oxazole rings.[8] One example of the many substrates and conditions investigated is shown in Figure 1. Treatment of the α-acetoxy ether **1** with TMSBr in CH_2Cl_2 at 0 °C gave the tetrahydropyran **2** as a single axial-bromide isomer in excellent yield. Cyclization with more commonly used Lewis acids such as $AlBr_3$ or $TiBr_4$ produced ca. 1:2 mixtures of **2** and **3** in about 50% yield. Bromide **2** could be displaced with CsOAc to produce the equatorial acetate in 79% yield,[9] demonstrating one synthetic application of such intermediates. Thus, the cyclization promoted by TMSBr was more efficient than with the typical Lewis acids and unexpectedly generated the axial 4-bromo adduct **2**.

The outcome of the cyclization was intriguing, and we further investigated the reaction using deuterated substrate **1-d**. One explanation for the axial selectivity is that the reaction proceeded through a boat transition state with the expected anti addition across the alkene.[10] Conformational relaxation of the product would deliver the axial bromide. Substrate **1-d** was used to probe the transition state. Cyclization of **1-d** proceeded to give the axial bromide **2-d**, with the C3-deuterium in the axial position. The boat TS hypothesis can be ruled out by this experiment because it would result in an equatorial C3-deuterium. The cyclization, therefore, proceeds through a chair TS with an unexpected syn addition across the alkene.

Oxazole substrates have shown unusual reactivity patterns in Prins cyclizations,[8] and so a more representative substrate, compound **4**, was selected to investigate the reaction. Treatment of **4** with $SnBr_4$ under typical segment-coupling Prins cyclization conditions produced a 9:79 ratio of axial and equatorial products **5** and **6**.[7b] Cyclization with TMSBr under the conditions used with substrate **1** (entry 2) reversed the selectivity and produced a 71:7 ratio of products favoring the axial isomer **5**. Clearly the axial selectivity did not require the presence of an oxazole ring. The addition of lutidine in CH_2Cl_2 gave a much more selective cyclization and produced **5** as a single isomer in 98% yield (entry 3). Lutidine inhibited the cyclization in hexanes. The role of lutidine in enhancing stereoselectivity was to shut down the moderately diastereoselective HBr-catalyzed cyclization, which is presented in

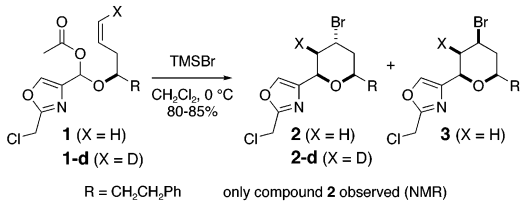
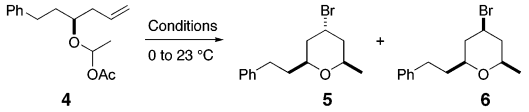


Figure 1. Treatment of α-acetoxy ether **1** leads to the axial 4-bromo tetrahydropyran **2**. Cyclization of deuterated **1-d** selectively produces the axial deuterated **2-d** (see text).

Table 1. Prins Cyclizations of α-Acetoxy Ether **4** Lead to Axial or Equatorial Products



entry[a]	Lewis acid	additive	solvent	yield **5** (%)	yield **6** (%)
1	$SnBr_4$	lutidine	CH_2Cl_2	9	79
2[c]	TMSBr	none	CH_2Cl_2	71	7
3[d]	TMSBr	lutidine	CH_2Cl_2	98	0
4	TMSBr	lutidine	hexanes	0	0
5[b]	HBr	none	CH_2Cl_2	60	27
6	AcBr	lutidine	CH_2Cl_2	96	0

[a] Reactions used 100 mg of **4**, 0.2 equiv of lutidine (when present), 2.5 equiv of Lewis acid in 2 mL of solvent, and were run at 0 °C (1 h) to 23 °C. Isolated yields are reported. [b] Excess HBr was used in the reaction. [c] GC analysis of the crude reaction mixture showed a 13:1 mixture of **5** and **6**. [d] GC analysis of the crude reaction mixture showed a 41:1 mixture of **5** and **6**.

entry 5. Consideration of the mechanism (vide infra) suggested that acetyl bromide might act as in inexpensive substitute for TMSBr, and this indeed proved to be the case, with selective formation of axial bromide **5** resulting (entry 6). Thus, the TMSBr-promoted cyclization works with a typical Prins cyclization substrate, and the addition of lutidine enhances the selectivity.

The scope of the reaction was investigated, Table 2. Both TMSBr and TMSI led to axial-selective Prins cyclization of α-acetoxy ethers such as **4** in excellent yields (entries 1−6). Substrate **10** (entry 7) produced two axial iodides in an 80:14 ratio. The C5 methyl substituent has a smaller conformational bias than the C6-alkyl substituents present in the other substrates. Cyclization with 1,1-disubstituted alkene **13** (entry 8) gave the axial tertiary bromide product **14**.[11] Heteroatoms are tolerated in the cyclization (entry 9), although *β*-alkoxy groups led to lower yields than other substrates (entry 10). The *E*-alkene **19** showed the expected axial selectivity, but the *Z*-alkene **21** generated a 2.5:1 ratio favoring the axial product (entries 11 and 12). The *Z*-alkene **21** is the only substrate we have investigated that led to significant quantities of the equatorial halide; all other substrates gave the axial products with excellent selectivities and in good-to-excellent yields.

A mechanistic proposal for the axial-selective Prins cyclization is outlined in Figure 2. Treatment of α-acetoxy ether **4** with TMSBr

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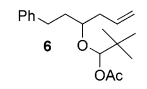
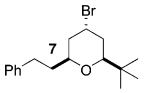
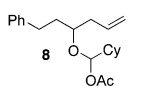
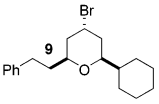
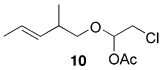
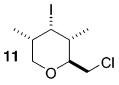
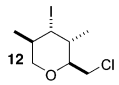
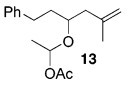
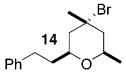
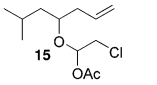
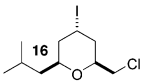
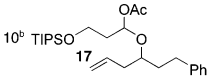
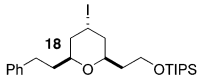
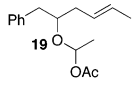
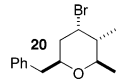
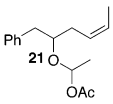
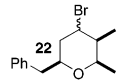
Table 2. Prins Cyclizations with TMSBr or TMSI Produce Axial 4-Halo tetrahydropyrans

entry[a]	SM	Lewis Acid	Product(s)	Yield(%)
1	**4**	TMSBr	**5** (X = Br)	98
2	**4**	TMSI	**5** (X = I)	92
3	 **6**	TMSBr	 **7**	92
4	**6**	TMSI	**7** (Br = I)	95
5	 **8**	TMSBr	 **9**	80
6	**8**	TMSI	**9** (Br = I)	92
7	 **10**	TMSI	 **11**	80
			 **12**	14
8	 **13**	TMSBr	 **14**	72
9	 **15**	TMSI	 **16**	94
10[b]	 **17**	TMSI	 **18**	64
11	 **19**	TMSBr	 **20**	92
12[c]	 **21**	TMSBr	 **22**	96

[a] Reactions run with 2.5 equiv of TMSBr or TMSI and 0.2 equiv of lutidine in CH_2Cl_2 at 0 °C for 1 h and then warming to 23 °C. [b] Reaction run at −20 °C for 5 min. [c] Axial/equatorial ratio was 2.5:1 for compound **22**.

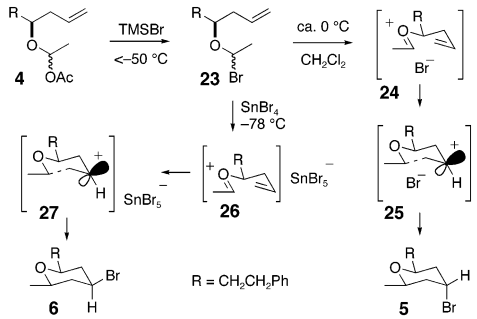


Figure 2. Mechanism for the formation of axial bromide **5** with TMSBr and the equatorial bromide **6** with $SnBr_4$ catalysis.

in CH_2Cl_2 at low temperature produced an intermediate that we have identified as the α-bromo ether.[12] Solvolysis of **23** provides the intimate ion pair **24**.[13] Cyclization to Alder's chair intermediate **25**, still as an intimate ion pair, and proximal addition of the bromide produces the observed axial adduct **5**. We are invoking a least motion pathway by the nucleophilic bromide in the cyclization.[14] The role of the lutidine is to shut down the less selective HBr-catalyzed cyclization (Table 1, entry 5). Further support for a mechanism involving solvolysis of an α-bromo ether comes from the cyclization of **4** with AcBr (Table 1, entry 6), a reagent commonly used to produce α-bromo ethers.[15]

The difference between this route and the cyclization pathway involving $SnBr_4$ is also illustrated in Figure 2. We found that treatment of the α-bromo ether intermediate with $SnBr_4$ at −78 °C produced a 1:1.4 mixture of axial **5** and equatorial **6**. The reversal of selectivity can be rationalized in the following way. Treatment of **23** with $SnBr_4$ leads to oxocarbenium ion **26** with $SnBr_5^-$ as the counterion. The $SnBr_5^-$ is much less nucleophilic than Br^-, thus allowing the formation of a solvent-separated ion pair.[13] As a result, bromide addition to Alder's cation **27** occurs from the preferred equatorial direction.[16]

We have developed the first axial-selective Prins cyclization. The reaction leads to excellent selectivities and good-to-excellent yields with a variety of substrates.

Acknowledgment. We thank the National Institutes of Health (CA081635) for their financial support.

Supporting Information Available: Representative examples of the TMSBr and TMSI Prins cyclizations and characterization of the α-bromo ether **23**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) A reviewer suggested an alternative explanation: the more stable nucleophile, $SnBr_5^-$, would have a later, product-like, transition state that would favor the equatorial product.

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