Divergent Diastereoselectivity in the Addition of Nucleophiles to Five-Membered-Ring Oxonium Ions

Jared T. Shaw and K. A. Woerpel*

Department of Chemistry, University of California, Irvine, California 92697-2025

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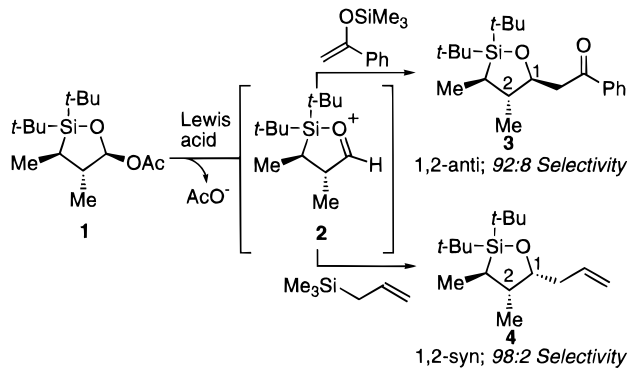
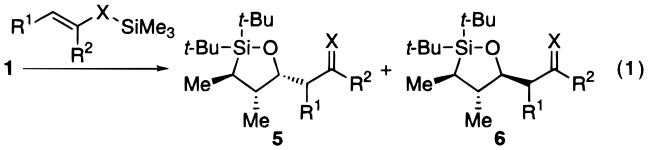
Nucleophilic addition to conformationally constrained electrophiles often results in highly stereoselective carbon−carbon bond formation. For example, reactions involving six-membered-ring electrophiles proceed with high stereoselectivity due to strong steric and stereoelectronic preferences.[1] These effects can be seen in many examples of addition to cyclic iminium and oxonium ions.[2−6] Reactions involving the analogous five-membered-ring intermediates in some cases show high diastereoselectivity, but a general, predictive explanation for the origin of selectivity is lacking.[7−11] In studying reactions of oxasilacyclopentane oxonium ions **2** (Scheme 1), we observed that the substitution pattern of the nucleophile determined the diastereoface that was attacked. Contrary to expectations, certain nucleophiles added with high diastereoselectivity to what appears to be the more hindered face. We report here our investigations of the divergent diastereoselectivity and a model to account for it. These results should contribute to the formulation of a general model to explain and predict the facial preferences for reactions involving five-membered-ring electrophiles.

Previous observations of the reactivity of oxasilacyclopentane acetates **1** demonstrated that the silyl enol ether of acetophenone added to **1** in the presence of a Lewis acid with high 1,2-anti selectivity (Scheme 1).[12] This outcome was expected by consideration of simple steric effects[13] and the topological similarities between the addition to oxonium ion **2** and Cram chelate addition.[14] While expanding the scope of this reaction to include other nucleophiles, we observed that the addition of allyltrimethylsilane showed the opposite preference, resulting in excellent 1,2-syn selectivity (Scheme 1). This dramatic reversal in selectivity revealed that the diastereoselectivities were not controlled by the alpha substituent[15] of the electrophile, but must be due to more subtle influences.[16−18]

Scheme 1



The facial selectivity does not depend on the type of nucleophilic alkene (allylsilane versus silyl enol ether) but is a function of the substitution pattern on the nucleophile (eq 1, Table 1).[19] Methallyltrimethylsilane, in a similar fashion to allyltrimethylsilane, added to **1** with high 1,2-syn selectivity (entry 2). Replacement of the methyl group of methallyltrimethylsilane with a phenyl group reversed the facial selectivity to provide the 1,2-trans product (entry 4). This divergence in facial selectivity was also observed with the analogous silyl enol ethers, with similarly high selectivities (compare entries 3 and 5 to entries 2 and 4). The introduction of a terminal substituent on the alkene led to predominantly 1,2-anti addition (entry 6), and a trisubstituted nucleophile also showed excellent 1,2-anti selectivity (entry 7).



(1)

The explanation for the divergent diastereoselectivity requires conformational analysis of oxonium ion **2**.[20] Molecular modeling suggests that the most stable conformation of **2** is best represented by the envelope shown in Figure 1. In this conformation, the dihedral angle between the oxygen and the α-methyl group is quite large (nearly 180°), and the dihedral angle between one *tert*-butyl group on silicon and the carbon of the oxonium ion is small (roughly 90°). Because of this small dihedral angle, the pseudoaxial *tert*-butyl group prevents nucleophilic attack from the top face; approach from this face would result in a destabilizing 1,3-diaxial interaction between the nucleophile and the *tert*-butyl group. The α-methyl group, positioned on the opposite face, lies too

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(15) The terms "alpha" and "beta" are used in this paper to denote the relative positions between the electrophilic carbon atom and the substituents on the ring.
(16) Control experiments confirmed that oxonium ion **2** was the reactive intermediate in this acetal substitution reaction; the details are provided as Supporting Information. For discussions of the mechanism of Lewis acid promoted acetal substitutions, see, for example: (a) Mori, I.; Ishihara, K.; Flippin, L. A.; Nozaki, K.; Yamamoto, H.; Bartlett, P. A.; Heathcock, C. H. *J. Org. Chem.* **1990**, *55*, 6107−6115. (b) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6458−6467.
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Table 1. Diastereoselectivity with Various Nucleophiles (eq 1)

	R^1	R^2	X	selectivity (**5**:**6**)[b]	yield (%)
1	H	H	CH_2	98:2	92
2	H	Me	CH_2	94:6	93
3	H	Me[c]	O	96:4	60
4	H	Ph	CH_2	11:89	91
5	H	Ph[c]	O	8:92	79
6	Me[d]	H	CH_2	14:86	91
7	Me[e]	Et	O	3:97	100

[a] CH_2Cl_2, 1 equiv of $SnBr_4$, −78° to 22 °C, unless otherwise noted. [b] Based on GC analysis. [c] $SnCl_4$ used as promoter. [d] >99% *Z* alkene. The major product (**6**) was formed as a mixture of diastereomers (80:20). [e] 98% *E* alkene. The major product (**6**) was formed as a mixture of diastereomers (95:5).

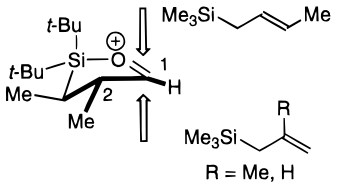
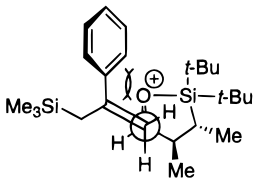


Figure 1.

close to the plane of the oxonium ion to exert much influence on the selectivity. Reactions with smaller nucleophiles (such as allyltrimethylsilane) reveal this inherent facial bias of the oxonium ion, attacking in a 1,2-syn fashion (Figure 1). Sterically demanding nucleophiles (Table 1, entries 6 and 7), in contrast, experience a direct destabilizing interaction with the α-methyl group in the transition state leading to the 1,2-cis product. This interaction must be destabilizing enough to override the inherent facial bias, so large nucleophiles attack in a 1,2-anti fashion (Figure 1).

In the case of the phenyl-substituted nucleophiles (Table 1, entries 4 and 5), the conformation of the nucleophile becomes an important factor in determining the sense of facial selectivity. Allyltrimethylsilane and methallyltrimethylsilane likely react through a synclinal transition state[21] in order to minimize steric interaction with the ring substituents. On the other hand, 1-(trimethylsilyl)-2-phenylpropene experiences benzylic strain between the alkene and arene, forcing the two planar groups to adopt a skewed orientation.[22] This increase in the effective size of the nucleophile destabilizes the synclinal transition state **7**, forcing approach from an antiperiplanar orientation as in **8**. In this transition state, the alpha center of the electrophile directs the facial selectivity, resulting in 1,2-anti addition. The same argument would apply to the analogous silyl enol ether (Table 1, entry 5).



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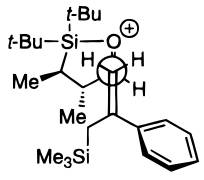
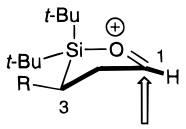


8

Based upon the hypothesis that the pseudoaxial *tert*-butyl group on silicon determines the inherent diastereoselectivity of nucleophilic addition to oxonium ion **2**, several predictions were made regarding the monosubstituted analogs of **2**, that is, **9** and **10**. As before, an envelope conformation was predicted for **9** and **10**, and in each case molecular models indicated that the pseudoequatorial isomers were most stable. Therefore, the *tert*-butyl groups in **9** and **10** were expected to direct approach of allyltrimethylsilane with 1,3-anti selectivity[10] for **9** and 1,2-syn selectivity for **10**.



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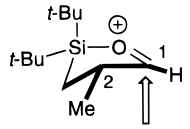
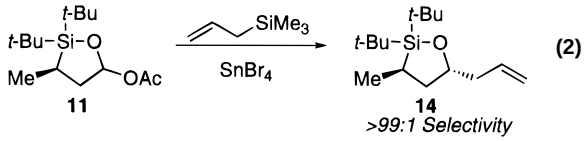
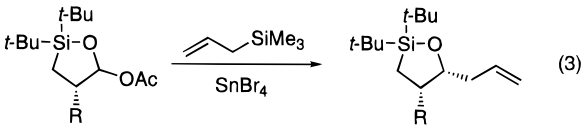


10

Monosubstituted oxasilacyclopentane acetates **11** and **12** were prepared,[13] and the selectivities that were predicted through conformational analysis of the oxonium ions were borne out by experiment (eqs 2 and 3). The β-methyl acetate **11** showed high selectivity,[10] indicating that a single beta substituent effectively locks the conformation of the electrophile (eq 2). Similarly, the α-methyl substrate **12** showed high 1,2-syn selectivity. This stereochemical result stands in stark contrast to 1,2-anti selective additions observed for simple γ-lactol substrates[10] and for reactions that are believed to proceed through five-membered-ring chelates.[23] To demonstrate the powerful influence exerted by the silicon *tert*-butyl groups, the α-isopropyl derivative **13** was prepared and nucleophilic substitution was performed (eq 3). Once again, the 1,2-cis product predominated, although the larger isopropyl group attenuated the stereoselectivity.



11 **14**
>99:1 Selectivity



12, R = Me
13, R = *i*-Pr

15, R = Me, *92 : 8 Selectivity*
16, R = *i*-Pr, *79 : 21 Selectivity*

It is apparent from the results presented here that the nucleophilic additions to five-membered-ring electrophiles can be quite selective. The inherent facial selectivity is not directly controlled by the substituent alpha to the electrophilic carbon center but is the consequence of strong conformational preferences and the seemingly more distant *tert*-butyl groups. We are currently employing this model to predict and rationalize other reactions which proceed via five-membered-ring oxonium ions.

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Supporting Information Available: Full experimental and analytical details and stereochemistry proofs. Details of the X-ray structure for Table 1, entry 7, are also provided (40 pages).

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