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Continuum of Mechanisms for Nucleophilic Substitutions of Cyclic Acetals

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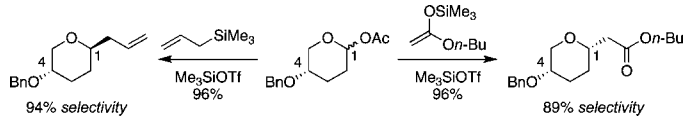
ABSTRACT



The effect of nucleophile strength on diastereoselectivity in the nucleophilic substitution of cyclic acetals was explored. Stereoselectivity remained constant and high as nucleophilicity increased until a threshold value was reached. Beyond this point, however, selection of Lewis acid determined whether stereochemical inversion or erosion was observed.

The development of stereocontrolled glycosylation reactions is complicated by the fact that these processes may proceed by S_N1-like[1−3] or S_N2-like[4−10] mechanisms. Changes in the glycosyl donor,[11,12] nucleophile,[13,14] activator,[15] and solvent[16] can alter selectivity unpredictably. This report documents the relationship between nucleophile strength and stereoselectivity for the substitution reactions of cyclic acetals; we describe dramatic changes in stereoselectivity and provide mechanistic rationales for these findings. This study provides insight applicable to the development of new stereoselective glycosylation reactions.

Acetal **1** was treated with a panel of nucleophiles having known nucleophilicity parameters (*N*)[17] in the presence of Me_3SiOTf (Table 1). A nucleophile's *N* value is a direct measure of reactivity: *N* correlates logarithmically with rates of reactions with carbocationic electrophiles.[17] Reactions with π-nucleophiles spanning more than four orders of magnitude of nucleophilicity led to selective formation of 1,4-*trans* products (entries 1 and 2). A roughly 100-fold further increase in *N*, however, associated with application of silylketene acetal nucleophiles **9**−**11**, resulted in reversal of diastereoselectivity: 1,4-*cis* products were formed selectively (entries 3−5). This dichotomy in stereochemical outcomes suggests a change in reaction mechanism.[18]

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(12) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681–1690.
(13) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815–6818.
(14) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.
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(18) A control experiment was performed to verify that diastereomer ratios resulted from kinetic product distributions under these reaction conditions. An isolated sample of *trans*-**4** was treated with silylketene acetal **11** (4.0 equiv) and Me_3SiOTf (1.6 equiv) under standard reaction conditions. The ester *trans*-**4** did not react under these conditions: neither stereochemical inversion to *cis*-**4** nor chemical exchange to form *cis*- or *trans*-**6** was observed.

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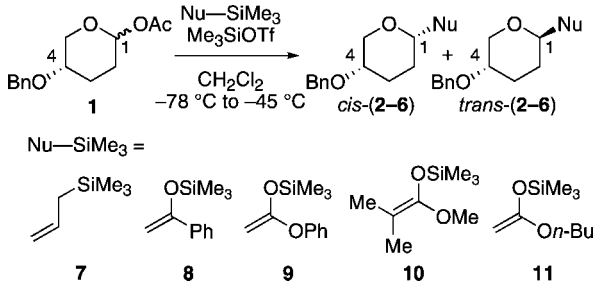
Table 1. Nucleophile Screen with Me_3SiOTf

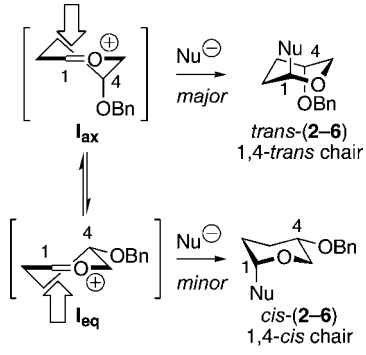


entry	Nu–$SiMe_3$	N^a	product	cis/trans[b,c]	yield[d] (%)
1	**7**	1.8	**2**	6:94	96
2	**8**	6.2	**3**	10:90	95
3	**9**	8.2	**4**	71:29	83
4	**10**	9.0	**5**	85:15	93
5	**11**	10.2	**6**	89:11	96

[a] N = nucleophilicity parameter; see ref 17. [b] Determined by GC and ^1H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Diastereoselectivities were independent of starting anomer ratio. [d] Isolated yield.

We have reported previously an electrostatic model to explain the trans selectivities observed in the reactions of acetal **1** with weak nuceophiles (e.g., **7** and **8**).[19,20] These reactions occur by S_N1-type mechanisms involving oxocarbenium ion intermediate **I** (Scheme 1).[21] Axial attack on the

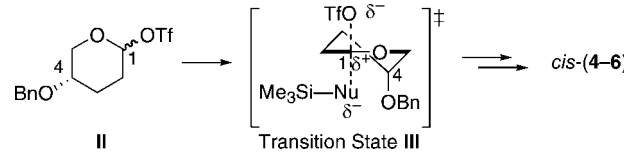
Scheme 1. Electrostatic Stereochemical Model



electrostatically preferred axial conformer $\mathbf{I_{ax}}$ affords trans products via a chairlike transition state. This model, however, does not account for the cis selectivities observed when strong nucleophiles **9**−**11** react with **1**. It is unlikely that the 1,4-*cis* ester products *cis*-(**4**−**6**) arise from disfavored equatorial conformer $\mathbf{I_{eq}}$ because increased nucleophile strength should not alter the conformational equilibrium of the oxocarbenium ion. Moreover, the selectivities of reactions of $\mathbf{I_{ax}}$ and $\mathbf{I_{eq}}$ should be independent of nucleophile reactivity unless reaction rates approach the diffusion limit.[22]

The stereochemical inversion observed in Me_3SiOTf-activated reactions of electrophile **1** with silylketene acetals **9**−**11** can be explained by S_N2-like substitutions[23−27] of triflate-trapped contact ion-pairs[28] **II** via transition state **III** (Scheme 2). Transition state **III** is consistent with the

Scheme 2. Proposed Transition State for S_N2-like Pathway



electrostatic model. As the triflate group departs from the axial orientation, the transition state (**III**) would develop significant carbocationic character at C1.[9,10] This accumulation of charge would cause the C4-benzyloxy group to adopt an axial orientation to stabilize the charge.[19,20] Together, these explanations account for the observed selectivity.[29]

In contrast to the results using Me_3SiOTf, nucleophilic substitution reactions of acetal **1** mediated by $BF_3{\cdot}OEt_2$ appeared to proceed via S_N1-like mechanisms regardless of nucleophile strength (Table 2). As observed with Me_3SiOTf, reactions of relatively weak π-nucleophiles **7** and **8** led to selective formation of 1,4-*trans* products with $BF_3{\cdot}OEt_2$ (entries 1 and 2). Application of silylketene acetal nucleophiles **9**−**11** to the $BF_3{\cdot}OEt_2$-mediated reactions of **1**, however, led to loss of stereoselectivity (entries 3−5). It is possible that these low selectivities reflect competition between S_N2-like and S_N1-like reaction mechanisms. The borate anions formed in the $BF_3{\cdot}OEt_2$-mediated reactions, however, are likely to coordinate quite poorly, disfavoring S_N2-like processes.[30] Further, unselective reactions were obtained with all three silylketene acetal nucleophiles (**9**−**11**)

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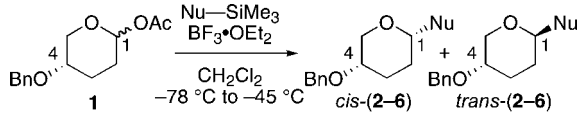
(29) This argument implies one of two possible scenarios: (a) The formation of anomeric triflates **II** occurs irreversibly to favor the trans isomer diastereoselectively, as observed in analogous nucleophilic additions to oxocarbenium ions (refs 19 and 20). The resulting dominant trans triflate isomer, then, undergoes stereospecific S_N2 substitution to form cis products. (b) Anomeric isomers of triflate **II** are formed reversibly and interconvert rapidly via an oxocarbenium ion intermediate, presumably in a solvent cage with the triflate counterion. Cis selectivity, in this case, arises from a preference for reaction through trans diaxial triflate **II**. Attempts to observe triflate **II** at low temperature have been unsuccessful thus far.

(30) Suzuki, S.; Matsumoto, K.; Kawamura, K.; Suga, S.; Yoshida, J. *Org. Lett.* **2004**, *6*, 3755–3758.

Table 2. Nucleophile Screen with $BF_3{\cdot}OEt_2$



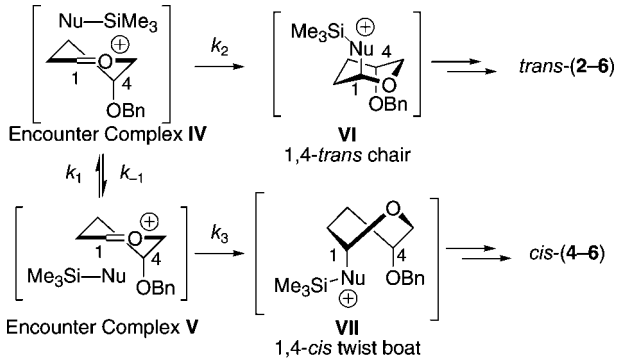
entry	Nu–$SiMe_3$	N^a	product	cis/trans[b,c]	yield[d] (%)
1	**7**	1.8	**2**	8:92	82
2	**8**	6.2	**3**	8:92	87
3	**9**	8.2	**4**	50:50	88
4	**10**	9.0	**5**	58:42	80
5	**11**	10.2	**6**	60:40	86

[a] N = nucleophilicity parameter; see ref 17. [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Diastereoselectivities were independent of starting anomer ratio. [d] Isolated yield.

despite differences in steric bulk and nucleophilicity; this finding suggests a statistical process.[31]

The loss of stereoselectivity in $BF_3{\cdot}OEt_2$-mediated reactions of **1** with silylketene acetal nucleophiles **9**−**11** can be explained by S_N1-like nucleophilic attack at the diffusion limit (Scheme 3).[22,32] Encounter complexes[24] **IV** and **V** are expected to form

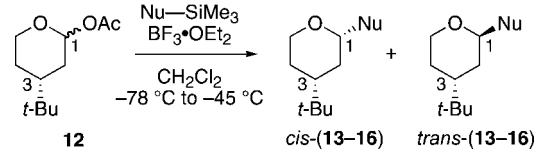
Scheme 3. Diffusion Limit Model



with no facial selectivity. If the rates of nucleophilic attack on the encounter complexes **IV** and **V** (k_2 and k_3) approach the rate of diffusion ($k_1 = k_{-1} \sim 10^9$ $M^{-1}s^{-1}$),[17,33] product ratios will reflect the initial statistical mixture of **IV** and **V**.[22,32] In this scenario, every nucleophile−electrophile collision leads to product, so no selectivity is observed.[34]

The model for loss of stereoselectivity depicted in Scheme 3 requires reaction via twist-boat intermediate **VII**. To test the viability of this intermediate, C3-*tert*-butyl acetal **12** was prepared and treated with a panel of nucleophiles under $BF_3{\cdot}OEt_2$ activation (Table 3). As observed for acetal **1**,

Table 3. Nucleophile Screen with Acetal **12**



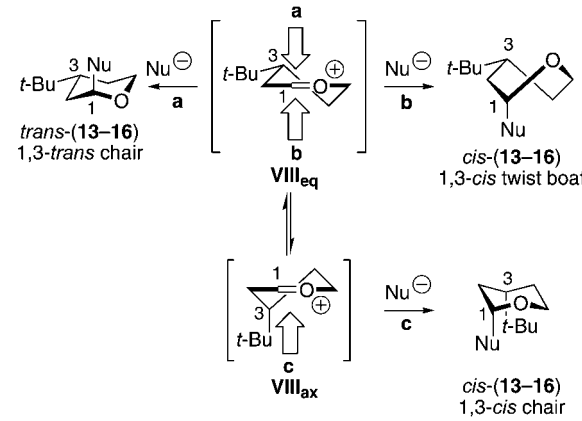
entry	Nu–$SiMe_3$	N^a	product	cis/trans[b,c]	yield[d] (%)
1	**7**	1.8	**13**	1:99	67
2	**8**	6.2	**14**	2:98	83
3	**9**	8.2	**15**	17:83	93
4	**11**	10.2	**16**	34:66	69

[a] N = nucleophilicity parameter; see ref 17. [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Diastereoselectivities were independent of starting anomer ratio. [d] Isolated yield.

stereoselectivities were high for relatively weak nucleophiles **7** and **8** but eroded with silylketene acetal nucleophiles **9** and **11**.[35]

The results in Table 3 are consistent with reaction via a twist-boat intermediate. Formation of the major 1,3-*trans* products arises from axial attack on equatorial conformer $\mathbf{VIII_{eq}}$ through a chairlike transition state (path a, Scheme 4). The minor 1,3-*cis* product is unlikely to arise by axial

Scheme 4. C3 *t*-Bu Stereochemical Model



attack on minor conformer $\mathbf{VIII_{ax}}$ through a chairlike transition state (path c). Not only should the $\mathbf{VIII_{ax}}$/$\mathbf{VIII_{eq}}$ conformational equilibrium favor equatorial conformer $\mathbf{VIII_{eq}}$,[36] but developing 1,3-diaxial interactions between the

(31) A control experiment was performed to verify that diastereomer ratios resulted from kinetic product distributions. An isolated sample of *cis*-**4** was treated with silylketene acetal **11** (4.0 equiv) and $BF_3{\cdot}OEt_2$ (1.6 equiv). The ester *cis*-**4** did not react under these conditions: neither stereochemical inversion to *trans*-**4** nor chemical exchange to form *cis*- or *trans*-**6** was observed.

(32) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677.

(33) Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6918–6928.

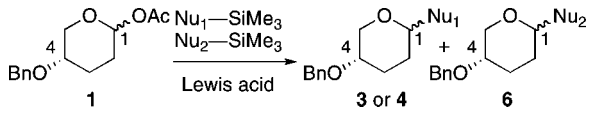
(34) We attribute the slight cis selectivity observed in the reaction of **10** and **11** with **1** under $BF_3{\cdot}OEt_2$-mediated conditions to ion pairing with the acetate counterion. This hypothesis is buttressed by our results with the pivaloate substrate **17** (vide infra).

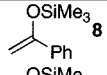
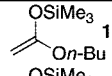
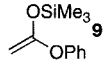
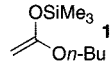
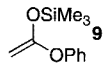
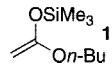
incoming nucleophile and the axial C3-*tert*-butyl group of $\mathbf{VIII}_{ax}$ should also block substitution by path c. Consequently, cis products are more likely formed by path b, which involves a twist-boat intermediate.

We next sought further evidence to support the stereochemical models developed for C4-benzyloxy acetal **1**. A series of competition experiments between nucleophiles was used to probe both the diffusion-limited rate hypothesis developed for reactions involving BF_3•OEt_2 (Scheme 3) and the S_N2-like pathway invoked in the case of Me_3SiOTf (Scheme 2). If at least one of the two nucleophiles involved in a competition experiment reacts with a rate below the diffusion limit, chemoselectivity should be observed.[22] This condition should obtain for all reactions of nucleophiles **7** and **8** and for the reactions that proceed by S_N2-like reaction paths. Conversely, if both nucleophiles in a competition experiment react with rates at or near the diffusion limit, as proposed in the case of **9**−**11** with BF_3•OEt_2, no chemoselectivity should be observed.[22]

As a control experiment, acetal **1** was treated with an equimolar mixture of enoxysilane nucleophile **8** ($N = 6.2$) and silylketene acetal **11** ($N = 10.2$) in the presence of BF_3•OEt_2 (Table 4, entry 1).[37] As expected, a small fraction

Table 4. Effect of Nucleophile on Chemoselectivity.



entry	Nu_1–$SiMe_3$[a]	Nu_2–$SiMe_3$[a]	Lewis acid	product ratio[b]
1	 **8**	 **11**	BF_3•OEt_2	**3**(4):**6**(96)
2	 **9**	 **11**	BF_3•OEt_2	**4**(25):**6**(75)
3	 **9**	 **11**	Me_3SiOTf	**4**(13):**6**(87)

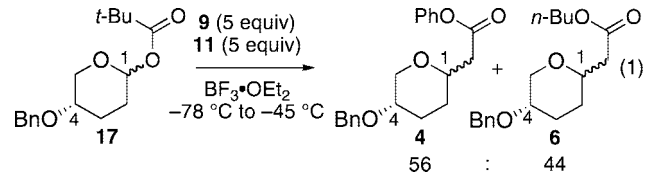
[a] 5 equiv of nucleophile. [b] Determined by GC spectroscopic analysis of the unpurified reaction mixture.

of **3** was formed, indicating that the enoxysilane **8** did not react with the electrophile at a rate near the diffusion limit.

The chemoselectivity observed when silylketene acetals **9** ($N = 8.2$) and **11** ($N = 10.2$) reacted with **1** in the presence of Me_3SiOTf (Table 4, entry 3) also implies non-diffusion-limited rates of nucleophilic attack. Triflate-trapped species **II** should be less electrophilic than oxocarbenium ion encounter complexes **IV/V**.[9,10] Consequently, S_N2-type nucleophilic substitution reactions in the presence of triflate anion should occur with rates below the diffusion limit. As noted previously, the stereochemical results with these nucleophiles (Table 1, entries 3 and 5) are consistent with reaction through transition state **III** (vide supra).

The results of treatment of **1** with silylketene acetals **9** and **11** in the presence of BF_3•OEt_2 suggested simultaneous operation of both S_N2-type and diffusion-limited S_N1-type paths. In this reaction, products **4** and **6** were formed in a 25:75 ratio (Table 2, entry 2), suggesting participation of a $[BF_3-OAc]^-$ counterion in the reaction with **11**.

To eliminate the potential for ion pairing, acetal **17**, bearing a pivaloate group, was examined. The steric bulk of the pivaloate group should decrease its ability to coordinate, thereby pushing the reaction completely to an S_N1-type mechanism. The reaction of **17** with **9** and **11** was unselective: a 56:44 ratio of **4** to **6** (eq 1) was obtained.[38] This result confirms the exclusive operation of a diffusion-limited S_N1-type mechanism when **9** and **11** react with the free oxocarbenium ion **IV/V** derived from pivaloate **17**.



We have described the effects of varying nucleophile strength on the stereochemical outcomes of acetal substitution reactions. Stereoselective S_N1-type mechanisms occur with weak and moderate nucleophiles and poor leaving groups, and unselective diffusion-limited S_N1 mechanisms and stereoselective S_N2 reaction pathways emerge with strong nucleophiles.

Acknowledgment. This research was supported by the National Institutes of Health, National Institute of General Medical Sciences (Grant GM-61066 to K.A.W. and Grant GM-081996 to J.R.K.). W.A.S. thanks the ARCS foundation for a fellowship. K.A.W. thanks Amgen and Lilly for generous support of research. We thank Dr. Phil Dennison (UCI) for assistance with NMR spectroscopy and Dr. John Greaves and Ms. Shirin Sorooshian (UCI) for mass spectrometry.

Supporting Information Available: Experimental procedures and compound characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(35) We hypothesize that for the reactions of silylketene acetals with oxocarbenium ion $\mathbf{VIII}_{eq}$, addition to the top face (pathway a) is at the diffusion limit, while addition to the bottom face (pathway b) occurs with a rate that is slightly below the diffusion limit. This scenario leads to a reduced, but not completely eroded, selectivity.

(36) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267–3268.

(37) Diastereoselectivities were consistent with the data in Tables 1 and 2.

(38) All substitutions of pivaloate **17** gave diastereoselectivities similar to those of acetate **1**, as detailed in the Supporting Information.