JOC Featured Article

pubs.acs.org/joc

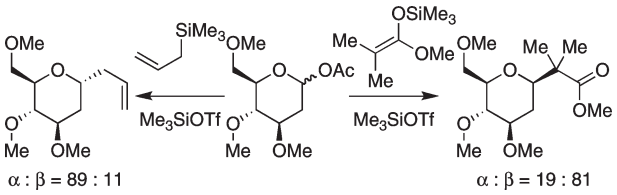
Correlations Between Nucleophilicities and Selectivities in the Substitutions of Tetrahydropyran Acetals

Jennifer R. Krumper, Walter A. Salamant, and K. A. Woerpel*

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

kwoerpel@uci.edu

Received July 28, 2009



Selectivities that deviate from S_N1 stereoelectronic models in the nucleophilic substitutions of tetrahydropyran acetals were investigated. When weak nucleophiles were employed, stereoselectivities conformed to known S_N1 stereoelectronic models. In contrast, stereoselectivities in the substitutions of acetals with strong nucleophiles depended on reaction conditions. Erosions in selectivities were observed when strong nucleophiles were employed in the absence of coordinating counterions. These erosions in selectivities are attributed to rates of nucleophilic additions to oxocarbenium ion intermediates that approach the diffusion limit. When triflate counterions were present, however, S_N2-like pathways became accessible with strong nucleophiles. In most cases examined, the major stereoisomers formed from reactions that proceeded through S_N2-like pathways were opposite to the major stereoisomers formed from the analogous reactions that proceeded through S_N1 pathways.

Introduction

The nucleophilic substitution reactions of functionalized tetrahydropyran acetals and related pyranosyl donors can proceed by either S_N1-[1−5] or S_N2-like[6−13] pathways. Deviation in the stereochemical outcomes of two similar pyranosyl substitutions can result from a change in the reaction mechanism. For example, allylation of a mannosyl donor, which likely proceeds through an S_N1 mechanism, afforded the α-pyranoside as the major stereoisomer,[14] while selectivity for the *β*-pyranoside in the allylation of a modified mannosyl donor is attributed to reaction through an S_N2-like mechanism.[15,16] Significant effort, particularly in carbohydrate synthesis, has been expended to develop conditions that favor a single pathway in a predictive manner.[7,17−23]

(1) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1992**, *114*, 10998–10999.
(2) Sammakia, T.; Smith, R. S. *J. Am. Chem. Soc.* **1994**, *116*, 7915–7916.
(3) Garcia, B. A.; Gin, D. Y. *J. Am. Chem. Soc.* **2000**, *122*, 4269–4279.
(4) Boebel, T. A.; Gin, D. Y. *J. Org. Chem.* **2005**, *70*, 5818–5826.
(5) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157–1160.
(6) The term "S_N2-like" encompasses both nucleophilic displacement of a covalently bound leaving group and nucleophilic addition to a contact ion-pair in which one face of an oxocarbenium ion intermediate is blocked by a counterion.
(7) Kim, J.-H.; Yang, H.; Park, J.; Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090–12097.
(8) Nukada, T.; Berces, A.; Zgierski, M. Z.; Whitfield, D. M. *J. Am. Chem. Soc.* **1998**, *120*, 13291–13295.
(9) Berces, A.; Enright, G.; Nukada, T.; Whitfield, D. M. *J. Am. Chem. Soc.* **2001**, *123*, 5460–5464.
(10) Fan, E.; Shi, W.; Lowary, T. L. *J. Org. Chem.* **2007**, *72*, 2917–2928.
(11) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951–7958.
(12) Crich, D.; Chandrasekera, N. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5386–5389.
(13) El-Badri, M. H.; Willenbring, D.; Tantillo, D. J.; Gervay-Hague, J. *J. Org. Chem.* **2007**, *72*, 4663–4672.
(14) Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545–9554.
(15) Crich, D.; Sharma, I. *Org. Lett.* **2008**, *10*, 4731–4734.
(16) Allylation of mannosyl phosphate with no selectivity has been reported: Singh, G.; Vankayalapati, H. *Tetrahedron: Asymmetry* **2001**, *12*, 1727–1735.
(17) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506–4507.
(18) McGarvey, G. J.; LeClair, C. A.; Schmidtmann, B. A. *Org. Lett.* **2008**, *10*, 4727–4730.
(19) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198–1199.
(20) Lam, S. N.; Gervay-Hague, J. *Org. Lett.* **2003**, *5*, 4219–4222.
(21) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056–4062.
(22) Codée, J. D. C.; de Jong, A. R.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *Tetrahedron* **2009**, *65*, 3780–3788.
(23) Dinkelaar, J.; de Jong, A. R.; van Meer, R.; Somers, M.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *J. Org. Chem.* **2009**, *74*, 4982–4991.

DOI: 10.1021/jo901639b Published on Web 10/08/2009

For example, changes in the pyranosyl donor,[17,22−24] nucleophile,[25−28] activator,[3,24] and solvent[29] can alter the predominant mechanistic pathway and the resulting stereoselectivity.

Stereoselectivity in tetrahydropyran acetal substitutions that proceed through S_N1 pathways can be predicted, or rationalized, by stereoelectronic models involving half-chair oxocarbenium ions.[30−32] In accord with Curtin−Hammett kinetics,[33] the facial preference of nucleophilic addition onto a substituted cyclic oxocarbenium ion depends upon which diastereomeric half-chair conformer is preferred and any developing interactions (e.g., 1,3-diaxial interactions) between the incoming nucleophile and the ring substituents.[34] These stereochemical models fail when the rates of nucleophilic addition to the intermediate oxocarbenium ion approach the diffusion limit.[35,36]

The major stereoisomers generated by S_N2-like nucleophilic substitutions of tetrahydropyran acetals can be predicted on the basis of the configurations at C1 of the tetrahydropyran donors. The lower energy chair conformations of donors that can undergo S_N2-like displacements, such as tetrahydropyran triflates,[3,37,38] iodides,[20,27] and fluorides,[11] typically favor axial conformations for the leaving groups at the anomeric (C1) positions.[4,38,39] Subsequent stereospecific displacements of these axial leaving groups with inversion account for the major stereoisomers observed in these transformations. Conditions and substrates that favor reaction through either the tetrahydropyran donor or a contact ion-pair over a solvent-separated oxocarbenium ion are critical to access S_N2-like pathways instead of S_N1 pathways.[4,17,40]

In this paper, we analyze the impact of nucleophile reactivity on the stereoselectivities of tetrahydropyran acetal substitutions and discuss mechanistic implications of these trends. We present evidence that suggests the substitutions of acetals with weak nucleophiles generally favor S_N1 mechanisms regardless of the conditions employed. In contrast, the mechanisms and stereochemical outcomes in the substitutions of acetals with strong nucleophiles appear highly dependent on which activator ($BF_3\cdot OEt_2$ or Me_3SiOTf) and which tetrahydropyran acetal are employed.

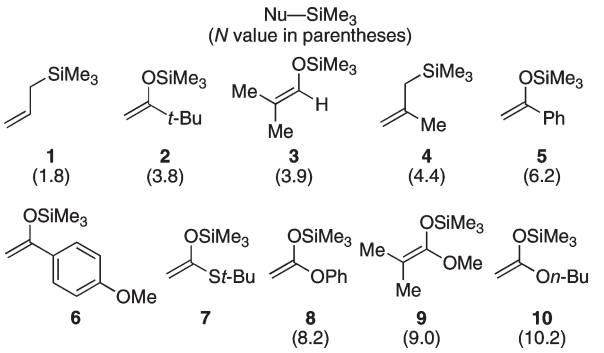


FIGURE 1. π-Nucleophile panel.

Experimental Approach

To investigate the influence of nucleophilicity on stereoselectivity in the substitutions of tetrahydropyran acetals, a series of neutral π-nucleophiles with varying nucleophilicities was selected (Figure 1).[41,42] The nucleophilicity values (*N*), derived by Mayr and co-workers, correlate logarithmically with rates of reactions with carbocationic electrophiles.[41,43] The nucleophiles selected for this study represent a range in reactivity that spans over eight orders of magnitude,[41] from the least reactive, allyltrimethylsilane **1** ($N = 1.8$), to the most reactive, alkylsilyl ketene acetal **10** ($N = 10.2$). Although the nucleophilicity values of enoxy silane **6** and silyl thioketene acetal **7** are unknown, we hypothesized they would lie between 6.2 and 8.2.[44]

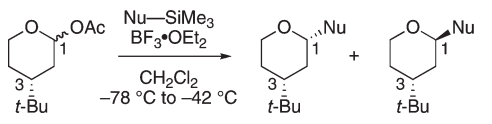
Results and Discussion

C3 *tert*-Butyl Acetal. Reactions of C3 *tert*-butyl acetal **11** with allyltrimethylsilyl or enoxy silane nucleophiles ($N = 1.8 - 6.2$) in the presence of $BF_3\cdot OEt_2$ afforded 1,3-trans stereoisomers with high selectivities (Table 1, entries 1−4). Although these reactions employed nucleophiles with reactivities spanning four orders of magnitude, stereoselectivities remained constant. When silyl ketene acetals **8** and **10** ($N = 8.2$ and 10.2, respectively) were employed, however, the major 1,3-trans stereoisomers were produced with eroded selectivities (Table 1, entries 5 and 6).

The loss of stereoselectivity in the substitution of acetal **11** with silyl ketene acetals **8** and **10** cannot be explained by a simple S_N1 stereochemical model[32] (Scheme 1). The 1,3-trans stereoisomers observed as the major products of the substitutions of acetal **11** with allyltrimethylsilyl and enoxy silane nucleophiles **1**, **2**, **4**, and **5** are assumed to result from

(24) Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553–1565.
(25) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815–6818.
(26) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293–4308.
(27) Gervay, J.; Hadd, M. J. *J. Org. Chem.* **1997**, *62*, 6961–6967.
(28) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679–11685.
(29) Vankar, Y. D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron* **1991**, *47*, 9985–9992.
(30) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032–7035.
(31) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289–296.
(32) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221.
(33) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.
(34) Lucero, C. G.; Woerpel, K. A. *J. Org. Chem.* **2006**, *71*, 2641–2647.
(35) Shenoy, S. R.; Smith, D. M.; Woerpel, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 8671–8677.
(36) Krumper, J. R.; Salamant, W. A.; Woerpel, K. A. *Org. Lett.* **2008**, *10*, 4907–4910.
(37) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223.
(38) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J.-i. *J. Am. Chem. Soc.* **2007**, *129*, 10922–10928.
(39) Displacements of equatorial triflates at the anomeric position have been reported to be favored over displacements of axial triflates: Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289–4296.
(40) Crich, D.; Li, L. *J. Org. Chem.* **2007**, *72*, 1681–1690.
(41) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66–77.
(42) Tokuyasu, T.; Mayr, H. *Eur. J. Org. Chem.* **2004**, 2791–2796.
(43) Mayr and co-workers have elucidated an additional nucleophile parameter, *s*, that we omit for the sake of clarity. Although the *s* value can have a significant impact on the predicted rate of a nucleophile−electrophile combination, the impact on relative rates between two different nucleophile−electrophile combinations is minimal if the *s* values are similar. The known *s* values for nucleophiles used in this study range from 0.79 to 1.0; see ref 41.
(44) The relative reactivities of enoxy silane **6** and silyl ketene thioacetal **7** to other nucleophiles employed in this study are estimated based upon reactivities of related compounds detailed by Mayr and co-workers (e.g., furan is more nucleophilic than thiophene); see ref 41. These estimated relative reactivities can also be inferred by reaction times in Mukaiyama aldol and Mannich reactions; see: (a) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. *J. Am. Chem. Soc.* **1999**, *121*, 669–685. (b) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, *10*, 917–920. (c) Hamada, T.; Manabe, K.; Kobayashi, S. *Chem.−Eur. J.* **2006**, *12*, 1205–1215. (d) Díez, E.; Prieto, A.; Simon, M.; Vázquez, J.; Alvarez, E.; Fernández, R.; Lassaletta, J. M. *Synthesis* **2006**, 540–550.

TABLE 1. Nucleophilic Substitution of C3 *tert*-Butyl Acetal 11 Activated by $BF_3 \cdot OEt_2$

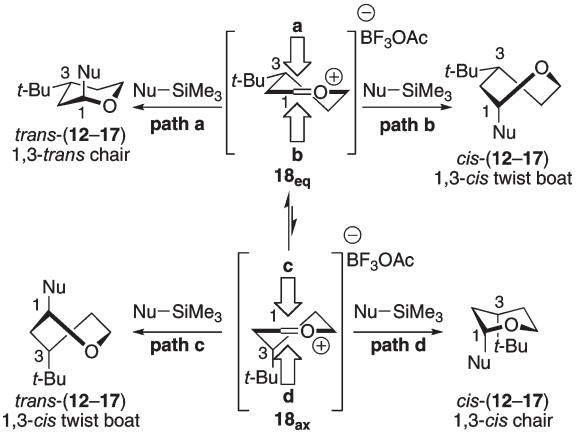


11 cis-(12–17) trans-(12–17)

entry	$Nu-SiMe_3$	N^a	product	*cis*/*trans*[b]	yield[c] (%)
1	**1**	1.8	**12**	1:99	67
2	**2**	3.8	**13**	1:99	88
3	**4**	4.4	**14**	1:99	80
4	**5**	6.2	**15**	2:98	83
5	**8**	8.2	**16**	17:83	93
6	**10**	10.2	**17**	34:66	69

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield.

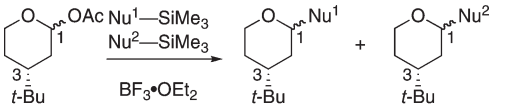
SCHEME 1. Stereoelectronic Model for Oxocarbenium Ion 18



nucleophilic additions to the stereoelectronically preferred face[32] of lower energy oxocarbenium ion conformer[45] $\mathbf{18_{eq}}$ (Scheme 1, path a). In contrast, the 1,3-cis stereoisomers observed when silyl ketene acetals **8** and **10** are employed can arise from either nucleophilic addition to the stereoelectronically disfavored face of the lower energy conformer $\mathbf{18_{eq}}$ (path b) or nucleophilic addition to the higher energy conformer $\mathbf{18_{ax}}$ (path d). Nucleophilic attack on the bottom face of minor conformer $\mathbf{18_{ax}}$ (path d) is discounted because a significant 1,3-diaxial interaction between the C3 *tert*-butyl group and the incoming nucleophile develops in the transition state. On the basis of this analysis, the two diastereomeric products arise from competitive addition to both faces of conformer $\mathbf{18_{eq}}$ (paths a and b).

Extrapolation of the work of Mayr and co-workers suggests that the loss of stereoselectivity observed in the substitutions of acetal **11** could occur if reaction rates approach the diffusion limit ($k \approx 10^9\ M^{-1}\ s^{-1}$).[41,46,47] The diffusion limit represents the maximum rate at which a bimolecular reaction can occur.[48] Application of this concept to the stereoelectronic model for oxocarbenium ion $\mathbf{18_{eq}}$ implies that erosion of stereoselectivity

TABLE 2. Competition Reactions with Acetal 11



11 13 or 16 15–17

entry	$Nu^1–SiMe_3$[a]	$Nu^2–SiMe_3$[a]	ΔN	product ratio[b] (Nu^1:Nu^2)
1	 **2**	 **5**	2.4	10:>90
2	 **2**	 **8**	4.4	5:>95
3	 **8**	 **10**	2.0	24:76

[a] Five equivalents of nucleophile. [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture.

occurs when the rates of reactions by both paths a and b approach the diffusion limit (Scheme 1). A statistical mixture of stereoisomers is expected when all viable reaction paths reach the diffusion limit.[46]

It was predicted that selectivity in a competition reaction between two nucleophiles with a single oxocarbenium ion electrophile (e.g., **18**) would corroborate that the loss of stereoselectivity in the addition of a nucleophile to a cyclic oxocarbenium ion results from diffusion-limited reaction rates. A competition experiment in which the rates of reaction are below the diffusion limit should favor the product generated from the more reactive znucleophile.[46] The selectivity in this competition reaction should reflect the logarithmic difference between the nucleophilicities of the two nucleophiles (ΔN).[43] For example, a difference of one order of magnitude between two different nucleophiles ($\Delta N = 1$) should result in an approximate 10:1 difference in rates between the two nucleophile−electrophile combinations.[43] If two nucleophiles both react at or near the diffusion limit, however, then a competition reaction between these two nucleophiles with a single electrophile should give a mixture of the two products regardless of the difference in nucleophilicities.[46,49]

A series of competition experiments were performed with acetal **11** and several pairs of nucleophiles to explore the diffusion-limit hypothesis (Table 2).[50] Treatment of acetal **11** with nucleophiles **2** and **5** in the presence of $BF_3 \cdot OEt_2$ afforded tetrahydropyran **15** in high selectivity (Table 2, entry 1). Tetrahydropyran **16** was obtained in high selectivity when nucleophiles **2** and **8** were used in competition (Table 2, entry 2). When two silyl ketene acetal nucleophiles (**8** and **10**) were employed, however, tetrahydropyrans **16** and **17** were produced with selectivity lower than predicted by

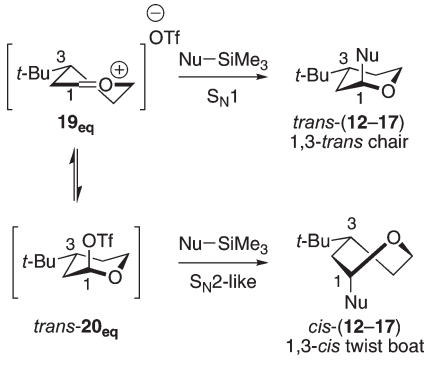
(45) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267–3268.
(46) Mayr, H.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844–1854.
(47) Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6918–6928.
(48) Atkins, P.; de Paula, J. *Physical Chemistry*; 7th ed.; Freeman: New York, 2002; pp 951-954.

(49) A third scenario is also possible: a competition reaction between two nucleophiles with a single electrophile would still be selective if only one nucleophile−electrophile combination proceeds with a rate near the diffusion limit. In this case, the major product would arise from the more reactive nucleophile, but the selectivity would be less than the expected from the difference in nucleophilicities (ΔN).
(50) Ratios of stereoisomers for all products observed in the competition experiments matched those observed in the individual reactions of a single nucleophile with a single acetal.

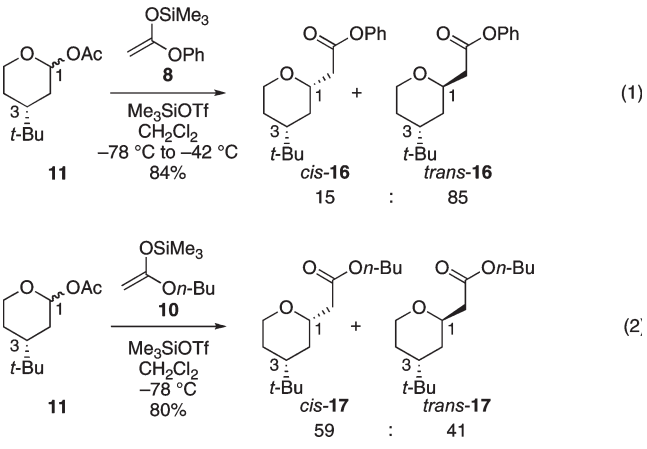
the difference in the nucleophilicity values of **8** and **10** (Table 2, entry 3). These results are consistent with the conclusion that nucleophiles **2** and **5** add to oxocarbenium ion $\mathbf{18_{eq}}$ with rates below the diffusion limit, but nucleophiles **8** and **10** add to oxocarbenium ion $\mathbf{18_{eq}}$ near the diffusion limit.

Based upon observations by Crich and co-workers,[37] we hypothesized that activation of acetal **11** with Me_3SiOTf, instead of $BF_3\cdot OEt_2$, might form tetrahydropyran triflate *trans*-$\mathbf{20_{eq}}$ in situ (Scheme 2). Tetrahydropyran triflate *trans*-$\mathbf{20_{eq}}$ is predicted to be the preferred isomer because steric strain is minimized when the C3 *tert*-butyl group adopts an equatorial position,[45] and anomeric donation from the endocyclic oxygen atom into the σ^* of the C1−OTf bond is maximized when the triflate is in an axial position.[38,51−53] In contrast to nucleophilic addition to oxocarbenium ion $\mathbf{19_{eq}}$ by an S_N1 pathway, nucleophilic attack on tetrahydropyran triflate *trans*-$\mathbf{20_{eq}}$ would provide 1,3-cis products as the major stereoisomers (Scheme 2).

SCHEME 2. Potential Mechanistic Pathways Involving Triflate Anion



Acetal **11** was treated with Me_3SiOTf in the presence of either silyl ketene acetal **8** or **10**. Reaction with silyl ketene acetal **8** afforded *trans*-**16** as the major diastereomer in a ratio similar to that observed for the reaction activated by $BF_3\cdot OEt_2$ (eq 1). On the other hand, the reaction of the more nucleophilic silyl ketene acetal **10** afforded *cis*-**17** as the major stereoisomer, albeit in low selectivity (eq 2). These two Me_3SiOTf-mediated reactions of acetal **11** suggest a transition from a single S_N1 mechanism in operation with silyl ketene acetal **8** (eq 1) to multiple mechanisms (competing S_N1 and S_N2-like pathways) in operation in the case of silyl ketene acetal **10** (eq 2).



C4 OBn Acetal. Inductive effects could alter the ratio of the solvent-separated oxocarbenium ion intermediate (associated with the S_N1 pathway) to the tetrahydropyran triflate intermediate (associated with the S_N2-like pathway).[37,40] Destabilization of a solvent-separated oxocarbenium ion (e.g., $\mathbf{19_{eq}}$, Scheme 2) would likely increase the relative concentration of the related tetrahydropyran triflate (e.g., *trans*-$\mathbf{20_{eq}}$).[40] This change in equilibrium would increase the likelihood of accessing an S_N2-like pathway.[40] Destabilization of a solvent-separated oxocarbenium ion would also increase the likelihood of the competitive S_N1 pathway approaching diffusion-limited rates.[46] Consistent with this hypothesis, oxygenation of tetrahydropyran acetals is known to reduce the rate of ionization due to inductive destabilization of the intermediate oxocarbenium ions.[54−57]

To probe the influence of inductive effects on the displacement reactions, substitutions of alkoxy-functionalized tetrahydropyran acetals were examined.[58] Nucleophilic substitution reactions of C4 OBn acetal **21** in the presence of $BF_3\cdot OEt_2$ resulted in a stereoselectivity trend similar to that observed in the substitutions of C3 *t*-butyl acetal **11** (Tables 1 and 3). Reactions of C4 OBn acetal **21** with enoxy silane **5** ($N = 6.2$) or weaker nucleophiles afforded 1,4-trans tetrahydropyrans as the major stereoisomers (Table 3, entries 1−4). Erosions in 1,4-trans selectivities were observed when more reactive nucleophiles enoxy silane **6** and silyl thioketene acetal **7** were employed (Table 3, entries 5 and 6). The use of silyl ketene acetal **8** ($N = 8.2$) afforded an equal mixture of stereoisomers (Table 3, entry 7). A slight preference for formation of the 1,4-cis stereoisomer was observed when the more reactive silyl ketene acetals **9** ($N = 9.0$) and **10** ($N = 10.2$) were employed (Table 3, entries 8 and 9).

The reactions of acetal **21** that proceed with high 1,4-trans selectivities (Table 3, entries 1−4) match the accepted stereoelectronic model (Scheme 3, paths a and d).[59,60] These high selectivities are observed when weak nucleophiles are employed, and the major 1,4-trans stereoisomers arise from stereoelectronically preferred additions to lower energy conformer $\mathbf{31_{ax}}$.[61−64]

(51) Efforts to observe tetrahydropyran triflates generated from Me_3SiOTf and the tetrahydropyran acetals employed in this study have been unsuccessful to date.

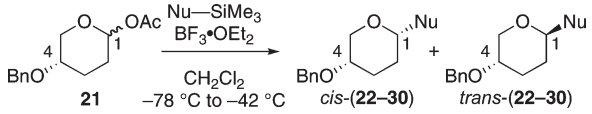
(52) Lemieux, R. U.; Koto, S. *Tetrahedron* **1974**, *30*, 1933–1944.
(53) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087.
(54) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270–1277.
(55) Withers, S. G.; Percival, M. D.; Street, I. P. *Carbohydr. Res.* **1989**, *187*, 43–66.
(56) Jensen, H. H.; Nordstrom, L. U.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 9205–9213.
(57) Jensen, H. H.; Bols, M. *Org. Lett.* **2003**, *5*, 3419–3421.

(58) Tetrahydropyran acetals with oxygen atom functionalization at C2 were not included in this study because the conditions employed to ionize the acetate acetals ($BF_3\cdot OEt_2$ or Me_3SiOTf in CH_2Cl_2 at temperatures of up to 0 °C) failed to ionize C2 alkoxy acetals.

(59) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168–169.
(60) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521–15528.
(61) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859–864.
(62) Miljković, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597–7604.
(63) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322–5323.

(64) Electrostatic effects on ring conformation equilibria and reactivity have been experimentally observed in related systems: (a) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259–265. (b) Bols, M.; Liang, X.; Jensen, H. H. *J. Org. Chem.* **2002**, *67*, 8970–8974. (c) McDonnell, C.; López, O.; Murphy, P.; Fernández Bolaños, J. G.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374–12385. (d) Jensen, H. H.; Lyngbye, L.; Jensen, A.; Bols, M. *Chem.−Eur. J.* **2002**, *8*, 1218–1226.

TABLE 3. Nucleophilic Substitution of Acetal 21 Activated by $BF_3 \cdot OEt_2$



entry	$Nu-SiMe_3$	N^a	product	*cis*/*trans*[b]	yield[c] (%)
1	**1**	1.8	**22**	8:92	83
2	**2**	3.8	**23**	11:89	84
3	**4**	4.4	**24**	10:90	57
4	**5**	6.2	**25**	8:92	87
5	**6**	NA	**26**	18:82	67
6	**7**	NA	**27**	21:79	93
7	**8**	8.2	**28**	50:50	88
8	**9**	9.0	**29**	58:42	80
9	**10**	10.2	**30**	60:40	86

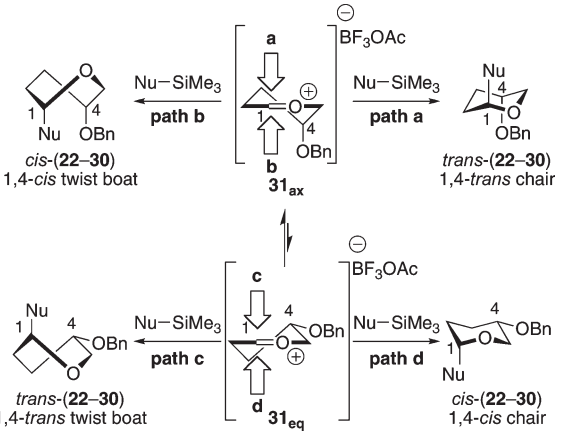
[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield. [d] Product was not isolated under these conditions.

(path a). The minor 1,4-cis stereoisomers likely arise from stereoelectronically preferred additions to higher energy conformer $\mathbf{31_{eq}}$ (path d).[59,60] Selectivities that conform to this model (Table 3, entries 1−4) are believed to reflect the ground-state ratio of conformers $\mathbf{31_{ax}}$ and $\mathbf{31_{eq}}$,[61,62] as described by a Winstein−Holness kinetic scenario (Scheme 3).[33]

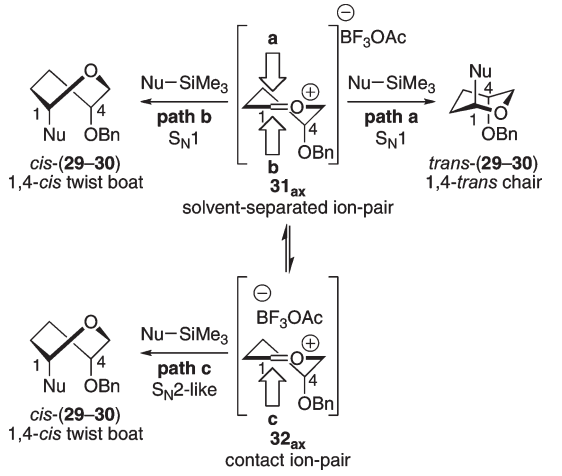
The erosion of selectivities in other reactions of acetal **21** (Table 3, entries 5−9) indicates a deficiency in the accepted stereoelectronic model (Scheme 3).[59,60] It is unlikely that the increased amounts of 1,4-cis stereoisomers result from stereoelectronic addition to higher energy conformer $\mathbf{31_{eq}}$ alone: nucleophilic strength should not alter the equilibrium of the oxocarbenium ion conformers. Similarly, there is no immediately obvious reason why addition to the stereoelectronically preferred face of higher energy conformer $\mathbf{31_{eq}}$ (path d) would become a lower energy pathway than addition to the stereoelectronically preferred face of lower energy conformer $\mathbf{31_{ax}}$ (path a) when strong nucleophiles are employed. The losses of stereoselectivities in these substitutions are most consistent with near-diffusion-limited rates of addition for both faces of oxocarbenium ions $\mathbf{31_{ax}}$ and $\mathbf{31_{eq}}$ (paths a−d).

The slight 1,4-cis selectivities observed when silyl ketene acetals **9** and **10** were employed (Table 3, entries 8 and 9) cannot be wholly rationalized by diffusion-limited additions of the nucleophile to oxocarbenium ion **31**. An emergent S_N2-like mechanism (Scheme 4, path c) could, however, account for increased formation of 1,4-cis stereoisomers. In these reactions, an S_N2-like mechanism requires the BF_3OAc^- counterion, which is typically considered to be noncoordinating,[65] to block one face of oxocarbenium ion **31**, likely as contact ion-pair **32**.[66−69] It is noteworthy in the

SCHEME 3. Stereoelectronic Model for Oxocarbenium Ion 31



SCHEME 4. Borate Contact Ion-Pair Model



context of this hypothesis that the starting anomer does not affect the observed selectivity in these reactions: starting with either *cis*-**21** or *trans*-**21** leads to the same ratio of stereoisomers.[70]

Acetal **21** was treated with a panel of nucleophiles in the presence of Me_3SiOTf to examine the influence of a triflate counterion on selectivity (Table 4). Substitution of C4 OBn acetal **21** with enoxy silane **5** (N = 6.2) or less reactive nucleophiles afforded 1,4-trans tetrahydropyrans as the major stereoisomers (Table 4, entries 1−4). The eroded stereoselectivities observed when enoxy silane **6** and silyl ketene thioacetal **7** were employed (Table 4, entries 5 and 6) also matched the selectivities in the analogous $BF_3 \cdot OEt_2$ mediated reactions (Table 3, entries 5 and 6). When silyl ketene acetals **8**−**10** were employed, however, the

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

(66) Winstein, S.; Grunwald, E.; Jones, H. W. *J. Am. Chem. Soc.* **1951**, *73*, 2700–2707.

(67) Winstein, S.; Klinedinst, P. E., Jr.; Robinson, G. C. *J. Am. Chem. Soc.* **1961**, *83*, 885–895.

(68) Huang, X.; Surry, C.; Hiebert, T.; Bennet, A. J. *J. Am. Chem. Soc.* **1995**, *117*, 10614–10621.

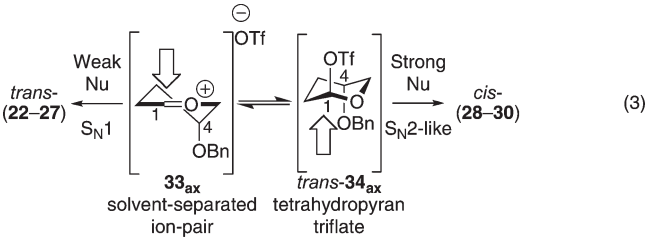
(69) Bennet, A. J.; Kitos, T. E. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1207–1222.

(70) This analysis implies that the diastereomeric contact ion-pairs generated from these tetrahydropyran acetals equilibrate faster than reactions of the contact ion-pairs with the nucleophile. A similar independence of starting anomeric ratios on stereoselectivities in related S_N2-like acetal substitutions have been reported. For example: (a) Reference 20. (b) Guindon, Y.; Ogilvie, W. W.; Bordeleau, J.; Cui, W. L.; Durkin, K.; Gorys, V.; Juteau, H.; Lemieux, R.; Liotta, D.; Simoneau, B.; Yoakim, C. *J. Am. Chem. Soc.* **2003**, *125*, 428–436.

(71) The stereoselectivities in the Me_3SiOTf-mediated substitutions of acetal **21** with silyl ketene acetals **8**−**10** were independent of the anomeric ratio of acetal **21**. Employing *cis*-**21**, *trans*-**21**, or a 50:50 mixture of anomers afforded identical results.

substitutions were selective for the 1,4-cis stereoisomers (Table 4, entries 7−9).[71,72]

Divergence in stereoselectivities in the Me_3SiOTf-activated substitutions of acetal **21** can be explained by three scenarios: stereoselective S_N1 pathways, diffusion-limited unselective S_N1 pathways, and S_N2-like pathways.[73−76] When weaker nucleophiles are employed (Table 4, entries 1−4), selectivity corresponds to the accepted stereoelectronic model of an S_N1 mechanism through solvent-separated oxocarbenium ion **33** (eq 3). Because the eroded selectivities with moderate strength nucleophiles **6** and **7** (Table 3, entries 5 and 6, and Table 4, entries 5 and 6) are the same regardless of which activator ($BF_3\cdot OEt_2$ or Me_3SiOTf) is used, the increased quantities of minor 1,4-cis stereoisomers are likely due to near diffusion-limited S_N1 processes rather than emergent S_N2-like pathways. When stronger nucleophiles, such as silyl ketene acetals **8**−**10**, are employed, S_N2-type displacements of tetrahydropyran triflate **34** occur to afford the 1,4-cis products (eq 3).

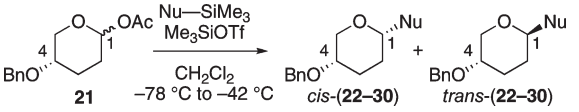


(3)

Selectivities for 1,4-cis stereoisomers in the substitutions of C4 OBn acetal **21** that follow S_N2-like pathways are consistent with an electrostatic model (Scheme 5) similar to that used to describe related S_N1 pathways (Scheme 3).[59,60] Kinetic isotope studies on related S_N2-like substitutions of pyranosyl donors indicate that significant cationic character develops at C1 in the transition state.[12,13,77,78] To account for this kinetic data, the S_N2-like substitutions of pyranosyl donors have been suggested to proceed through either "exploded" transition states (e.g., **35**) or contact ion-pairs (e.g., **36**).[12,13] Placement of the C4 OBn substituent axial in both "exploded" transition state **35** and contact ion-pair **36** maximizes the electrostatic interaction between the cationic center at C1 and the partially negative oxygen atom at C4.[61,62]

A series of competition experiments were performed with C4 OBn acetal **21** to support the mechanistic rationales presented for the nucleophilic substitutions of acetal **21**

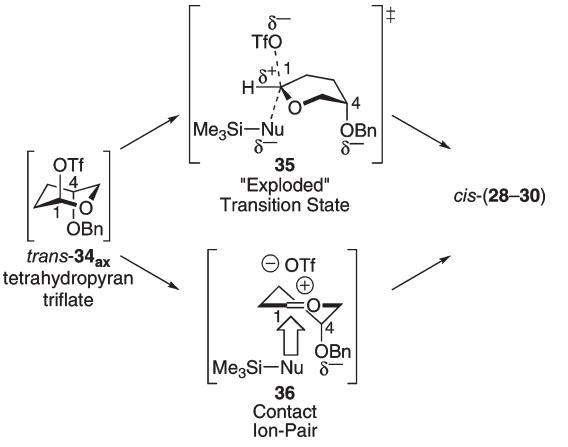
TABLE 4. Nucleophilic Substitution of Acetal 21 Activated by Me_3SiOTf



entry	Nu−$SiMe_3$	N^a	product	*cis*/*trans*[b]	yield[c] (%)
1	**1**	1.8	**22**	6:94	96
2	**2**	3.8	**23**	12:88	87
3	**4**	4.4	**24**	10:90	50
4	**5**	6.2	**25**	10:90	95
5	**6**	NA	**26**	18:82	NA[d]
6	**7**	NA	**27**	27:73	85
7	**8**	8.2	**28**	71:29	83
8	**9**	9.0	**29**	85:15	93
9	**10**	10.2	**30**	89:11	96

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^1H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield. [d] Product was not isolated under these conditions.

SCHEME 5. S_N2-like Pathway for Tetrahydropyran Triflate 34



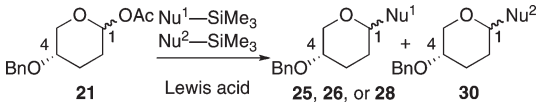
(Table 5).[50] When enoxy silane **5** (N = 6.2) was placed in competition with silyl ketene acetal **10** (N = 10.2), the product arising from reaction with the more reactive silyl ketene acetal **10**, tetrahydropyran **30**, was formed with high selectivity (Table 5, entry 1). This result indicates that the addition of enoxy silane **5** to intermediate oxocarbenium ion **31** is significantly below the diffusion-limited rate of addition of silyl ketene acetal **10**. In contrast, the eroded selectivity between enoxy silane **6** and silyl ketene acetal **10** with acetal **21** (Table 5, entry 2), combined with the eroded stereoselectivity observed in the reaction of enoxy silane **6** with acetal **21** (Table 3, entry 5), suggest a near diffusion-limited rate of addition of enoxy silane **6** to oxocarbenium ion **31**.

A $BF_3\cdot OEt_2$-mediated competition reaction between silyl ketene acetals **8** (N = 8.2) and **10** (N = 10.2) with C4 OBn acetal **21** resulted in low selectivity for products **28** and **30** (Table 5, entry 3). This low selectivity, which is below the theoretical 100:1 ratio (ΔN = 2.0), remains consistent with nucleophilic addition of both silyl ketene acetals **8** and **10** to oxocarbenium ion **31** to be near the diffusion limit. Because diffusion-limited reactions should afford statistical mixtures

(72) Two control experiments were performed to verify that diastereomer ratios resulted from kinetic product distributions under these reaction conditions. An isolated sample of *trans*-**28** was treated with silyl ketene acetal **10** (4.0 equiv) and Me_3SiOTf (1.6 equiv) under standard reaction conditions. The ester *trans*-**28** did not react under these conditions: neither stereochemical inversion to *cis*-**28** nor chemical exchange to form *cis*- or *trans*-**30** was observed. In addition, an isolated sample of *cis*-**28** was treated with silyl ketene acetal **10** (4.0 equiv) and $BF_3\cdot OEt_2$ (1.6 equiv) under standard reaction conditions. The ester *cis*-**28** did not react under these conditions either.

(73) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169.
(74) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689–4691.
(75) Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082–6095.
(76) Denmark, S. E.; Almstead, N. G. *J. Org. Chem.* **1991**, *56*, 6485–6487.
(77) Bennet, A. J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1986**, *108*, 7287–7294.
(78) Zhang, Y.; Bommuswamy, J.; Sinnott, M. L. *J. Am. Chem. Soc.* **1994**, *116*, 7557–7563.

TABLE 5. Competition Reactions with Acetal 21



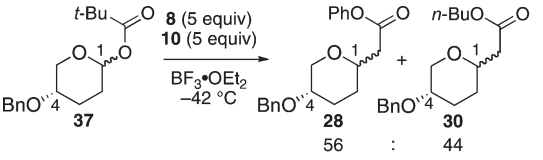
entry	Nu^1–$SiMe_3$[a]	Nu^2–$SiMe_3$[a]	ΔN	Lewis acid	product ratio[b] (Nu^1:Nu^2)
1	 **5**	 **10**	4.0	BF_3•OEt_2	4:96
2	 **6**	 **10**	NA	BF_3•OEt_2	19:81
3	 **8**	 **10**	2.0	BF_3•OEt_2	25:75
4	 **6**	 **10**	NA	Me_3SiOTf	3:97
5	 **8**	 **10**	2.0	Me_3SiOTf	13:87

[a]Five equivalents of nucleophile. [b]Determined by GC and ^1H NMR spectroscopic analysis of the unpurified reaction mixture.

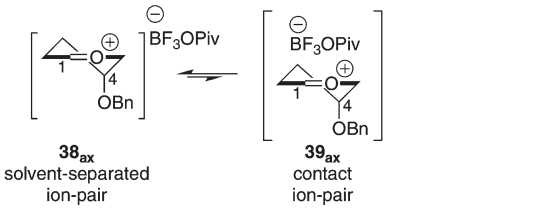
of products, however, the low selectivity observed in this competition experiment also supports an emergent S_N2-like mechanism (Scheme 4) as a viable alternative pathway to the S_N1 mechanism.

Competition experiments with acetal **21** activated by Me_3SiOTf in the presence of silyl ketene acetal **10** and one other nucleophile were designed to differentiate between Me_3SiOTf-mediated S_N2-like pathways and $BF_3\cdot OEt_2$-mediated S_N1 pathways. Selectivity between enoxy silane **6** and silyl ketene acetal **10** in the substitution of acetal **21** increased when the Lewis acid employed was changed from $BF_3\cdot OEt_2$ (Table 5, entry 2) to Me_3SiOTf (Table 5, entry 4). Similarly, a Me_3SiOTf-mediated competition reaction between silyl ketene acetals **8** and **10** (Table 5, entry 5) resulted in higher selectivity than the analogous $BF_3\cdot OEt_2$-mediated reaction (Table 5, entry 3). These results support S_N2-like pathways proceeding at rates below the diffusion limit, but in which the overall activation energies are lower than the alternative diffusion-limited S_N1 pathways. A corollary to this conclusion is that tetrahydropyran triflate *trans*-$\mathbf{34_{ax}}$ is lower in energy, and thus higher in concentration, than solvent-separated oxocarbenium ion $\mathbf{33_{ax}}$.[51]

A final competition experiment between silyl ketene acetals **8** and **10** was designed to favor only S_N1 pathways and minimize alternative S_N2-like pathways (eq 4). Ionization of pivaloate acetal **37** with $BF_3\cdot OEt_2$ should generate a cyclic oxocarbenium ion with a BF_3OPiv^- counterion. We hypothesized that the steric bulk of this borate counterion would serve to disfavor contact ion-pair $\mathbf{39_{ax}}$ and thus any S_N2-like pathways that would involve $\mathbf{39_{ax}}$ (eq 5). When acetal **37** was treated with $BF_3\cdot OEt_2$ in the presence of silyl ketene acetals **8** and **10**, a near-statistical mixture of tetrahydropyrans **28** and **30** was observed.[79] This lack of selectivity for the pivaloate (eq 4) as compared to the acetate (Table 5, entry 3) supports near diffusion-limited additions of nucleophiles **8** and **10** to solvent-separated oxocarbenium ion $\mathbf{38_{ax}}$.



(4)



(5)

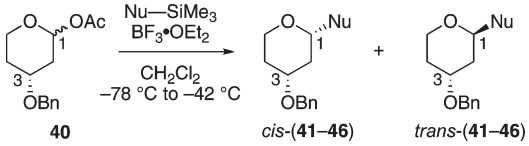
C3 OBn Acetal. We next examined the $BF_3\cdot OEt_2$-activated substitutions of C3 OBn acetal **40** with members of a panel of nucleophiles (Table 6). Similar to previous reports, allylation of acetal **40** afforded tetrahydropyran *cis*-**41** as the major stereoisomer (Table 6, entry 1).[59,60] Substitutions of acetal **40** with nucleophiles more reactive than allyltrimethylsilane **1** ($N = 1.8$) and less reactive than silyl ketene acetal **10** ($N = 10.2$), maintained modest, but lower, selectivities for the 1,3-cis stereoisomers (Table 6, entries 2−5). A decrease in stereoselectivity was again observed when C3 OBn acetal **40** was treated with $BF_3\cdot OEt_2$ in the presence of silyl ketene **10** (Table 6, entry 6).

The stereoselectivities in the substitutions of C3 OBn acetal **40** provide insight into our previously reported electrostatic stereochemical model[59,60] (Scheme 6). In this model, the major 1,3-cis stereoisomer arises from nucleophilic addition to the stereoelectronically preferred face[32] of lower energy conformer $\mathbf{47_{ax}}$[61,62] (Scheme 6, path b). The minor 1,3-trans stereoisomer results from nucleophilic addition to the stereoelectronically preferred face of higher energy conformer $\mathbf{47_{eq}}$ (path c). An increase in the quantity of 1,3-trans stereoisomer formed could result from diffusion-limited rates of addition to the stereoelectronically disfavored face of oxocarbenium ion $\mathbf{47_{ax}}$ (path a). Alternatively, developing 1,3-diaxial interactions between the C3 OBn group and the incoming nucleophile in the transition state of path b would become more severe with larger nucleophiles, which would lead to a greater relative preference for path c.

If the erosion of stereoselectivities observed in the substitutions of C3 OBn acetal **40** were solely due to reaction rates approaching the diffusion limit, then stereoselectivities should have steadily decreased as nucleophilicities increased.[46] This trend was not initially observed; stereoselectivities were modest but remained constant when nucleophiles **3**, **5**, **8**, and **9** were employed despite a range in reactivity of five orders of magnitude (Table 6, entries 2−5). The lower stereoselectivities observed in the substitutions of acetal **40**

(79) Both substitution reactions afforded near statistical mixtures of stereoisomers as well.

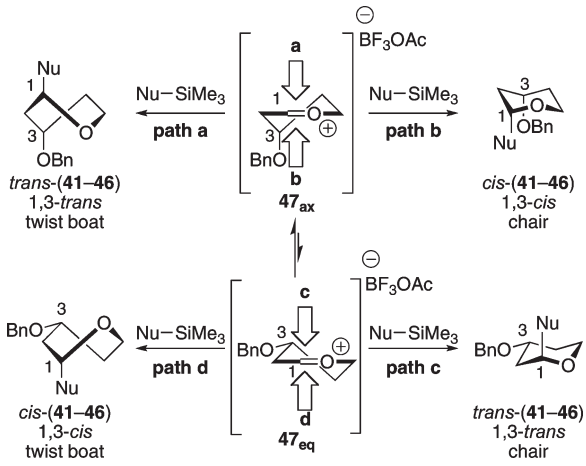
TABLE 6. Nucleophilic Substitution of Acetal 40 Activated by $BF_3 \cdot OEt_2$



entry	Nu−$SiMe_3$	N^a	product	*cis*/*trans*[b]	yield[c] (%)
1	**1**	1.8	**41**	88:12	70
2	**3**	3.9	**42**	79:21	98
3	**5**	6.2	**43**	79:21	92
4	**8**	8.2	**44**	80:20	93
5	**9**	9.0	**45**	77:23	97
6	**10**	10.2	**46**	63:37	96

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield.

SCHEME 6. Stereoelectronic Model for Oxocarbenium Ion 47



when nucleophiles **3**, **5**, **8**, and **9** were employed (Table 6, entries 2−5) instead of when allyltrimethylsilane **1** was employed (Table 6, entry 1) are likely due to a change in the steric bulk of the nucleophiles compared to allyltrimethylsilane **1**. In the context of this hypothesis, however, it is surprising that other nucleophile pairs with large steric differences (e.g., enoxy silanes **3** and **5** or silyl ketene acetals **8** and **9**) provided products with similar levels of stereoselection.

The low stereoselectivity observed when silyl ketene acetal **10** was employed (Table 6, entry 6), however, is consistent with rates of nucleophilic addition to oxocarbenium ion half-chairs $\mathbf{47_{ax}}$ and $\mathbf{47_{eq}}$ approaching the diffusion limit (Scheme 6). In this case, an increase in nucleophilicity corresponded to a lower observed selectivity. Because silyl ketene acetal **10** is no more bulky than nucleophiles **3**, **5**, **8**, or **9**, a steric argument does not sufficiently rationalize the low selectivity observed when silyl ketene acetal **10** was employed.

Acetal **40** was treated with several strong nucleophiles in the presence of Me_3SiOTf to evaluate if changing the counterion would result in stereoisomers originating from emergent S_N2-like pathways (Table 7). Based upon the trend observed with C4 OBn acetal **21** (Tables 3 and 4), the S_N2-like substitution pathway of C3 OBn acetal **40** was expected to favor formation of the opposite stereoisomer compared to the S_N1 pathway. In this case, the 1,3-trans tetrahydropyrans were expected to be the major stereoisomers instead of the 1,3-cis tetrahydropyrans observed as the major products in $BF_3 \cdot OEt_2$-mediated reactions. Instead, not only did the 1,3-cis tetrahydropyrans remain the major stereoisomers, but the 1,3-cis tetrahydropyrans were produced in higher selectivity when Me_3SiOTf was employed (Table 7) than when the reaction was performed with $BF_3 \cdot OEt_2$ (Table 6). This trend stands in marked contrast to the impact of employing Me_3SiOTf in the substitution reactions of C4 OBn acetal **21** (Tables 3 and 4).

The surprisingly high 1,3-cis selectivities observed in the Me_3SiOTf-activated substitutions of acetal **40** can be rationalized by considering hypothetical tetrahydropyran triflate intermediates and the S_N2-like reactions of these species (Scheme 7). Although displacement of tetrahydropyran triflate *cis*-**48** through contact ion-pair $\mathbf{49_{ax}}$ would maximize electrostatic stabilization between the cationic center at C1 and the electronegative C3 oxygen atom,[61,62] steric and electrostatic repulsion between the C3 oxygen atom and the triflate counterion would also be maximized.[80] In contrast, an S_N2-like displacement of tetrahydropyran triflate *trans*-**48** would account for increased 1,3-cis stereoselectivities in these transformations. It is unclear if the increase in 1,3-cis stereoisomers in Me_3SiOTf mediated reactions is the result of tetrahydropyran triflate *trans*-**48** being lower in energy than tetrahydropyran triflate *cis*-**48**, or if the S_N2-like substitution of tetrahydropyran triflate *trans*-**48** is faster than that of *cis*-**48**.

2-Deoxyglucose Acetal. Extension of these studies to 2-deoxyglucosyl acetal **50** provided a template for studying the influence of several ring oxygen atoms on substitution selectivities (Table 8). Unlike the previous monosubstituted acetals **11**, **21**, and **40**, the substitutions of 2-deoxyglucose acetal **50** required relatively elevated temperatures (0 °C).[81] Allylation of acetal **50** activated by $BF_3 \cdot OEt_2$ afforded **51α** as the major stereoisomer, correlating to the results of related allylation reactions.[82,83] Substitutions of acetal **50** with more reactive nucleophiles under these conditions, however, proved to be unselective.

Although the α-selectivity in the allylation of acetal **50** corresponds to the previously published stereochemical model,[82] the lack of selectivity with the other nucleophiles employed represent a critical failure of this model (Scheme 8). Developing 1,3-diaxial interactions in the transition state between the incoming nucleophile and axial substituents at C3 and C5 disfavor addition to the stereoelectronically preferred face of conformer $\mathbf{57_{ax}}$, despite evidence that the $^3H_4$ conformer $\mathbf{57_{ax}}$ is lower in energy than the $^4H_3$ conformer $\mathbf{57_{eq}}$[82] (Scheme 8, path c). In accord with Curtin−Hammett kinetics,[33] the major α-stereoisomer in the allylation of acetal **50** likely arises from

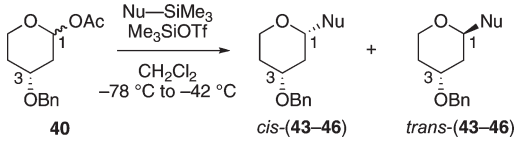
(80) de Oliveira, P. R.; Rittner, R. *Spectrochim. Acta, Part A* **2005**, *61*, 1737–1745.

(81) Selected substitutions were repeated at 0 °C and were observed to have slightly lower selectivities than when the same reactions were performed at −42 °C. Details are provided as Supporting Information.

(82) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545–553.

(83) Fujiwara, K.; Sato, D.; Watanabe, M.; Morishita, H.; Murai, A.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2004**, *45*, 5243–5246.

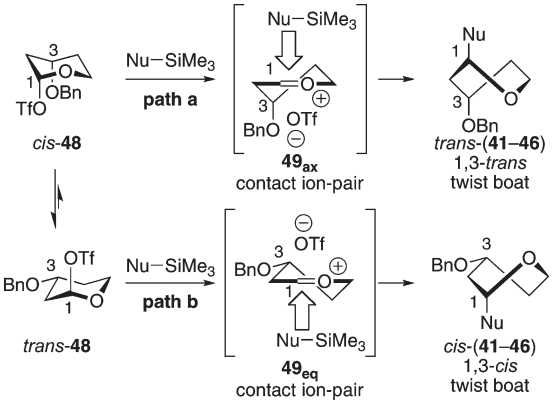
TABLE 7. Nucleophilic Substitution of Acetal 40 Activated by Me_3SiOTf



entry	Nu−$SiMe_3$	N^a	product	*cis*/*trans*[b]	yield[c] (%)
1	**1**	1.8	**41**	87:13	87
2	**5**	6.2	**43**	89:11	84
3	**8**	8.2	**44**	88:12	86
4	**10**	10.2	**46**	79:21	88

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield.

SCHEME 7. S_N2-like Pathways for Tetrahydropyran Triflate 48

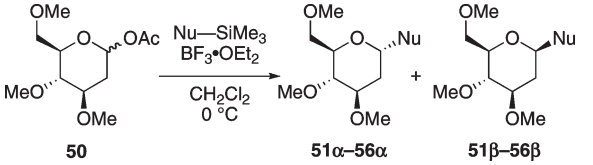


addition to the stereoelectronically preferred face of $^4H_3$ conformer $\mathbf{57_{eq}}$ (Scheme 8, path b). The increased ratios of β-stereoisomers observed when nucleophiles stronger than allyltrimethylsilane are employed may result from either addition to the stereoelectronically preferred face of $^3H_4$ conformer $\mathbf{57_{ax}}$ (path c), addition to the stereoelectronically disfavored face of $^4H_3$ conformer $\mathbf{57_{eq}}$ (path a), or both. Regardless of which pathway(s) is responsible for the formation of the β-stereoisomer, however, the erosion of selectivities observed is consistent with a near-diffusion-limited reaction rate for the pathway that produces the α-stereoisomer (path b).

The stereoselectivities in the substitutions of 2-deoxyglucosyl acetal **50** in the presence of Me_3SiOTf proved to be highly dependent on the nucleophile employed (Table 9). Allylation of acetal **50** with Me_3SiOTf, as with $BF_3\cdot OEt_2$ (Table 8, entry 1), afforded **51α** as the major stereoisomer (Table 9, entry 1). Similarly, the low stereoselectivities observed in the substitutions of acetal **50** with methallyltrimethylsilane **4** and enoxy silane **5** in the presence of Me_3SiOTf (Table 9, entries 2 and 3) matched the low selectivities observed in the analogous $BF_3\cdot OEt_2$ mediated reactions (Table 8, entries 2 and 3). When silyl ketene acetals **8** and **9** were employed in the reaction, however, β-stereoisomers **54*β*** and **55*β*** were generated with good selectivities (Table 9, entries 4 and 5).

As observed in the other systems described in this report, divergence in stereoselectivities in the Me_3SiOTf-activated

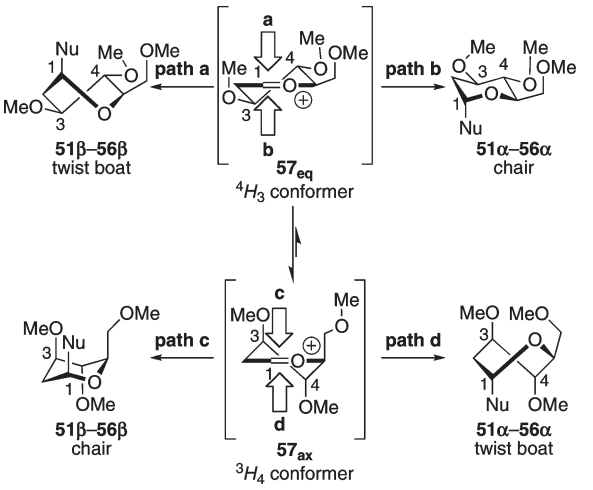
TABLE 8. Nucleophilic Substitution of Acetal 50 Activated by $BF_3\cdot OEt_2$



entry	Nu−$SiMe_3$	N^a	product	α/β^b	yield[c] (%)
1	**1**	1.8	**51**	89:11	80
2	**4**	4.4	**52**	43:57	79
3	**5**	6.2	**53**	61:39	83
4	**8**	8.2	**54**	45:55	83
5	**9**	9.0	**55**	43:57	57
6	**10**	10.2	**56**	NA	decomp.

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield.

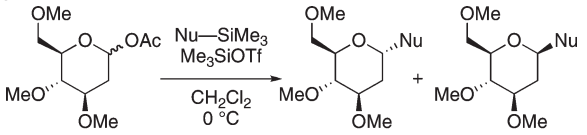
SCHEME 8. Stereoelectronic Model for Oxocarbenium Ion 57



substitutions of acetal **50** can be explained by a change from S_N1- to S_N2-like pathways (Scheme 9). When allyltrimethylsilane is employed (Table 9, entry 1), the selectivity observed suggests operation of an S_N1 mechanism (Scheme 8) and indicates reaction through solvent-separated oxocarbenium ion **57** rather than tetrahydropyran triflate **58**. The low selectivities in the substitutions of acetal **50** with nucleophiles **4** and **5** (Table 8, entries 2 and 3, and Table 9, entries 2 and 3), which are the same regardless of which activator ($BF_3\cdot OEt_2$ or Me_3SiOTf) is used, are likely the result of near-diffusion-limited S_N1 processes and not emergent S_N2-like pathways. This analysis is identical to the one used to rationalize the selectivities in the reactions of C4 OBn acetal **21** with nucleophiles **6** and **7** (Tables 3 and 4). When stronger nucleophiles, such as silyl ketene acetals **8** and **9**, are employed, S_N2 displacements of tetrahydropyran triflate **58α** occur to afford the β-stereoisomers (Scheme 9).[84]

(84) Because relatively warm temperatures (0 °C) were employed in the substitutions of acetal **50**, the reactive intermediate in the S_N2-like pathway may be a contact ion-pair rather than tetrahydropyran triflate **58α**. Pyranosyl triflates have been observed to be unstable on the NMR time scale above −50 °C (ref 38).

TABLE 9. Nucleophilic Substitution of Acetal 50 Activated by Me_3SiOTf

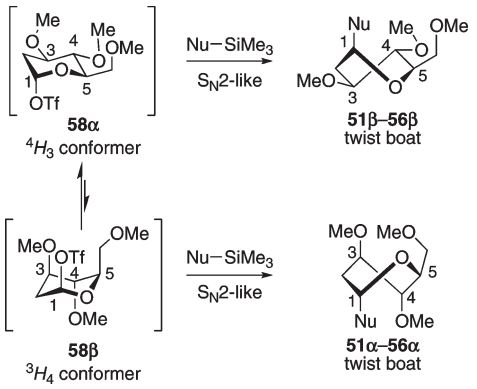


50 **51α–56α** **51β–56β**

entry	Nu−$SiMe_3$	N^a	product	α/β[b]	yield[c] (%)
1	**1**	1.8	**51**	89:11	57
2	**4**	4.4	**52**	50:50	73
3	**5**	6.2	**53**	68:32	94
4	**8**	8.2	**54**	27:73	78
5	**9**	9.0	**55**	19:81	68
6	**10**	10.2	**56**	NA	decomp.

[a] N = nucleophilicity parameter.[41] [b] Determined by GC and ^{1}H NMR spectroscopic analysis of the unpurified reaction mixture. [c] Isolated yield.

SCHEME 9. S_N2-like Displacement of Pyranosyl Triflate 58



Conclusions

Examination of the substitutions of tetrahydropyran acetals reveals a dramatic impact of nucleophile reactivity and the activating agent on the stereoselectivities of these transformations. When $BF_3\cdot OEt_2$ was employed, substitutions of acetals appeared to proceed largely through S_N1 mechanisms. Consequently, the selectivities in the nucleophilic additions to oxocarbenium ion intermediates follow stereoelectronic models developed for these S_N1 processes and remain constant as nucleophilicity is increased until a threshold nucleophilicity is reached. Beyond this point, however, selectivities decrease until a statistical mixture is obtained. This result is consistent with the emergence of diffusion-limited reaction rates above this increased nucleophile activity threshold.

In contrast, when Me_3SiOTf was employed in the substitution of tetrahydropyran acetals, S_N2-like pathways, likely through tetrahydropyran triflate intermediates, become competitive with S_N1 pathways when strong nucleophiles are employed. Although substitutions with weak nucleophiles still follow S_N1 mechanisms, substitutions with stronger nucleophiles, notably silyl ketene acetals **8**−**10**, appear to intercept either tetrahydropyran triflates or the associated contact ion-pairs through S_N2-like mechanisms. In this analysis, tetrahydropyran triflates or the associated contact ion-pairs are present when weak nucleophiles are employed. The lowest energy pathway with weak nucleophiles in the cases studied, however, involves nucleophilic attack of a solvent-separated oxocarbenium ion. Conditions that allow access of S_N2-like pathways in tetrahydropyran acetal substitutions represent a complementary technique to conditions that favor S_N1 pathways because the two mechanisms often favor opposite stereoisomers.

Experimental Section

General Procedure for Nucleophilic Substitution Reactions of Acetals 11, 21, 37, 40, and 50. To a cooled (−78 °C) 0.1 M solution of the acetal (0.4−0.8 mmol, 1.0 equiv) and nucleophile (2.0−4.0 equiv) in CH_2Cl_2 was added the Lewis acid (1.4−1.6 equiv) dropwise. After being stirred at −78 °C for 1−5 min, the reaction mixture was maintained at −42 °C for 1−2 h. A saturated aqueous solution of $NaHCO_3$ (4.0 mL) was added, and the solution was warmed to 22 °C. The resulting biphasic mixture was diluted with CH_2Cl_2 (2 mL) and H_2O (2 mL), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The standard procedure for nucleophilic substitution was modified when 2-deoxyglucose acetal **50** was employed: the reagents were combined at −42 °C and then allowed to stir at 0 °C for 1−2 h before addition of saturated $NaHCO_3$. Diastereomeric ratios were determined by GC and confirmed by GC/MS and ^{1}H NMR spectroscopy. Reported yields refer to purified material. The nucleophilic substitutions of acetal **21** activated by $BF_3\cdot OEt_2$ (Table 3) are reported here as representative examples.

2- Allyl-5-(benzyloxy)tetrahydro-2*H*-pyran (22).[59] The conditions for a standard nucleophilic substitution were followed with acetal **21** (0.102 g, 0.407 mmol), allyltrimethylsilane **1** (0.260 mL, 1.64 mmol), and $BF_3\cdot OEt_2$ (0.080 mL, 0.64 mmol). Analysis of the crude mixture revealed an 8:92 ratio of *cis*-**22** to *trans*-**22**. Purification by flash chromatography (2.5:97.5 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.078 g, 83%). Characterization matches reported values[59] and is reported for the isomer *trans*-**22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 5.80 (ddt, J = 17.2, 10.2, 7.0, 1H), 5.10−5.01 (m, 2H), 4.58 (d, J = 11.9, 1H), 4.52 (d, J = 11.9, 1H), 4.09 (ddd, J = 10.8, 4.7, 2.3, 1H), 3.43 (tt, J = 10.3, 4.6, 1H), 3.33−3.25 (m, 1H), 3.18 (t, J = 10.5, 1H), 2.30−2.22 (m, 1H), 2.22−2.12 (m, 2H), 1.78−1.70 (m, 1H), 1.49−1.38 (m, 1H), 1.36−1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 135.0, 128.6, 127.82, 127.78, 117.0, 77.1, 73.2, 70.94, 70.92, 40.4, 30.3, 30.2; HRMS (TOF MS ES+) m/z calcd for $C_{15}H_{20}NaO_2$ $(M + Na)^+$ 255.1361, found 255.1369.

1-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]-3,3-dimethylbutan-2-one (23). The conditions for a standard nucleophilic substitution were followed with acetal **21** (0.102 g, 0.407 mmol), enoxy silane **2** (0.293 g, 1.70 mmol), and $BF_3\cdot OEt_2$ (0.080 mL, 0.64 mmol). Analysis of the crude mixture revealed an 11:89 ratio of *cis*-**23** to *trans*-**23**. Purification by flash chromatography (5:95 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.099 g, 84%). Characterization is reported for the isomer *trans*-**23**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.58 (d, J = 11.9, 1H), 4.52 (d, J = 12.0, 1H), 4.03 (ddd, J = 10.8, 4.7, 2.3, 1H), 3.77 (dtd, J = 11.7, 6.4, 1.9, 1H), 3.43 (tt, J = 9.6, 4.6, 1H), 3.21 (t, J = 10.5, 1H), 2.80 (dd, J = 17.0, 6.6, 1H), 2.43 (dd, J = 17.0, 5.8, 1H), 2.18 (br d, J = 12.5, 1H), 1.79 (br d, J = 13.3, 1H), 1.55−1.44 (m, 1H), 1.28 (tdd, J = 13.4, 11.2, 3.8, 1H), 1.12 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.5, 138.6, 128.5, 127.7, 127.6, 73.7, 72.9, 70.8, 70.7, 44.3, 42.6, 30.5, 30.0, 26.2; IR (neat) 2966, 2868, 1707, 1454, 1365, 1097 cm^{-1};

HRMS (TOF MS ES+) m/z calcd for $C_{18}H_{26}NaO_3$ (M + Na)$^+$ 313.1780, found 313.1779.

5-(Benzyloxy)-2-(2-methylallyl)tetrahydro-2*H*-pyran (24). The standard procedure for nucleophilic substitution was followed with acetal **21** (0.127 g, 0.507 mmol), methallyltrimethylsilane **4** (0.350 mL, 1.99 mmol), and $BF_3 \cdot OEt_2$ (0.100 mL, 0.789 mmol). Analysis of the crude mixture revealed a 10:90 ratio of *cis*-**24** to *trans*-**24**. Purification by flash chromatography (2.5:97.5 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.0703 g, 57%). Characterization is reported for the isomer *trans*-**24**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36−7.24 (m, 5H), 4.79 (s, 1H), 4.73 (s, 1H), 4.58 (d, J = 11.9, 1H), 4.52 (d, J = 11.9, 1H), 4.10 (ddd, J = 10.8, 4.7, 2.3, 1H), 3.50−3.36 (m, 2H), 3.18 (t, J = 10.5, 1H), 2.24 (dd, J = 14.1, 7.5, 1H), 2.21−2.15 (m, 1H), 2.09 (dd, J = 14.1, 5.6, 1H), 1.74 (br s, 4H), 1.50−1.40 (m, 1H), 1.29 (tdd, J = 13.6, 11.0, 3.7, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.7, 138.7, 128.6, 127.82, 127.77, 112.6, 75.8, 73.2, 71.0, 70.9, 44.4, 30.7, 30.3, 22.8; IR (thin film) 3072, 3033, 2939, 2854, 1648, 1455 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{16}H_{22}NaO_2$ (M + Na)$^+$ 269.1518, found 269.1518.

2-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]-1-phenylethanone (25).[36] The standard procedure for nucleophilic substitution was followed with acetal **21** (0.099 g, 0.40 mmol), enoxy silane **5** (0.305 g, 1.59 mmol), and $BF_3 \cdot OEt_2$ (0.082 mL, 0.64 mmol). Analysis of the crude mixture revealed an 8:92 ratio of *cis*-**25** to *trans*-**25**. Purification by flash chromatography (10:90 EtOAc/hexanes) afforded the product as an oily, white solid (0.108 g, 87%). Characterization matches reported values[36] and is reported for the isomer *trans*-**25**: mp 59−60.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 7.9, 2H), 7.57 (t, J = 7.3, 1H), 7.46 (t, J = 7.7, 2H), 7.37−7.27 (m, 5H), 4.59 (d, J = 11.9, 1H), 4.53 (d, J = 11.9, 1H), 4.06 (ddd, J = 10.8, 4.6, 2.2, 1H), 3.98−3.88 (m, 1H), 3.48 (tt, J = 10.0, 4.5, 1H), 3.29 (dd, J = 16.3, 6.7, 1H), 3.24 (t, J = 10.6, 1H), 2.93 (dd, J = 16.3, 5.8, 1H), 2.27−2.18 (m, 1H), 1.97−1.87 (m, 1H), 1.60−1.48 (m, 1H), 1.46−1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.2, 138.7, 137.3, 133.4, 128.8, 128.6, 128.4, 127.9, 127.8, 74.2, 73.0, 71.0, 70.9, 44.7, 30.8, 30.2; IR (thin film) 3061, 2860, 2352, 1681, 1596 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{22}NaO_3$ (M + Na)$^+$ 333.1467, found 333.1460. Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.14; H, 7.07.

2-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]-1-(4-methoxyphenyl)-ethanone (26). The standard procedure for nucleophilic substitution was followed with acetal **21** (0.203 g, 0.811 mmol), enoxy silane **6** (0.762 g, 3.43 mmol), and $BF_3 \cdot OEt_2$ (0.165 mL, 1.30 mmol). Analysis of the crude mixture revealed an 18:82 ratio of *cis*-**26** to *trans*-**26**. Purification by flash chromatography (20:80 EtOAc/hexanes) afforded the product as a faint yellow solid (0.185 g, 67%). Characterization is reported for the isolated isomers *cis*-**26** and *trans*-**26**.

cis-**26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.8, 2H), 7.38−7.25 (m, 5H), 6.93 (d, J = 8.8, 2H), 4.59 (s, 2H), 4.06 (d, J = 12.5, 1H), 4.03−3.98 (m, 1H), 3.87 (s, 3H), 3.55 (d, J = 12.4, 1H), 3.42 (br s, 1H), 3.35 (dd, J = 16.3, 6.4, 1H), 2.93 (dd, J = 16.3, 6.0, 1H), 2.11−2.05 (m, 1H), 1.86−1.77 (m, 1H), 1.73−1.65 (m, 1H), 1.64−1.56 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.0, 163.7, 138.9, 130.8, 130.6, 128.6, 127.8, 127.7, 113.9, 74.3, 70.6, 70.2, 69.9, 55.7, 44.8, 27.1, 26.9.

trans-**26**: mp 69−70 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.7, 2H), 7.37−7.26 (m, 5H), 6.93 (d, J = 8.7, 2H), 4.59 (d, J = 11.9, 1H), 4.53 (d, J = 11.9, 1H), 4.09−4.03 (m, 1H), 3.93−3.89 (m, 1H), 3.86 (s, 3H), 3.47 (tt, J = 9.8, 4.4, 1H), 3.27−3.19 (m, 2H), 2.87 (dd, J = 15.9, 5.8, 1H), 2.21 (d, J = 12.3, 1H), 1.91 (d, J = 13.0, 1H), 1.57−1.48 (m, 1H), 1.44−1.35 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.7, 163.8, 138.7, 130.8, 130.4, 128.6, 127.9, 127.8, 113.9, 74.4, 73.1, 71.0, 70.9, 55.7, 44.3, 30.9, 30.2; IR (thin film) 3064, 3031, 2937, 2861, 1671, 1600 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{21}H_{24}NaO_4$ (M + Na)$^+$ 363.1572, found 363.1578. Anal. Calcd for $C_{21}H_{24}O_4$: C, 74.09; H, 7.11. Found: C, 74.24; H, 7.12.

***S*-*tert*-Butyl 2-[5-(benzyloxy)tetrahydro-2*H*-pyran-2-yl]ethanethioate (27).** The standard procedure for nucleophilic substitution was followed with acetal **21** (0.100 g, 0.400 mmol), thiosilyl ketene acetal **7** (0.198 g, 0.970 mmol), and $BF_3 \cdot OEt_2$ (0.080 mL, 0.64 mmol). Analysis of the crude mixture revealed a 21:79 ratio of *cis*-**27** to *trans*-**27**. Purification by flash chromatography (10:90 EtOAc/hexanes) afforded the product as a faint yellow oil (0.120 g, 93%). Characterization is reported for a 27:73 mixture of *cis*-**27** to *trans*-**27**: ^{1}H NMR (500 MHz, $CDCl_3$; the major *trans*-**27** isomer is denoted by *) δ 7.38−7.23 (m, 5H* + 5H), 4.57 (d, J = 12.1, 1H* + 2H), 4.51 (d, J = 12.0, 1H*), 4.10−4.02 (m, 1H* + 1H), 3.84−3.76 (m, 1H), 3.70 (dddd, J = 11.0, 7.4, 5.5, 2.0, 1H*), 3.49 (dd, J = 12.5, 1.4, 1H), 3.43 (tt, J = 10.1, 4.5, 1H*), 3.38 (br s, 1H), 3.19 (t, J = 10.5, 1H*), 2.80 (dd, J = 15.0, 7.0, 1H), 2.67 (dd, J = 14.8, 7.4, 1H*), 2.54 (dd, J = 15.0, 5.9, 1H), 2.48 (dd, J = 14.8, 5.5, 1H*), 2.17 (br d, J = 9.6, 1H*), 2.07−1.99 (m, 1H), 1.80−1.70 (m, 1H* + 1H), 1.62 (tt, J = 13.6, 3.7, 1H), 1.52−1.46 (m, 1H*), 1.44 (s, 9H* + 9H), 1.38−1.27 (m, 1H* +1H); ^{13}C NMR (125 MHz, $CDCl_3$; the major *trans*-**27** isomer is denoted by *) δ 198.0, 197.7*, 138.8, 138.6*, 128.6*, 128.5, 127.8*, 127.7* (minor isomer overlaps), 127.6, 74.21*, 74.16, 72.8*, 70.89*, 70.86*, 70.4, 70.1, 69.6, 50.9, 50.5*, 48.4*, 48.2, 30.4*, 30.0, 29.92*, 29.90*, 27.0, 26.4; IR (neat) 2960, 2861, 1681, 1454, 1095 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{18}H_{26}NaO_3S$ (M + Na)$^+$ 345.1500, found 345.1494. Anal. Calcd for $C_{18}H_{26}O_3S$: C, 67.04; H, 8.13. Found: C, 67.19; H, 8.33.

Phenyl 2-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]acetate (28).[36] The standard procedure for nucleophilic substitution was followed with acetal **21** (0.152 g, 0.607 mmol), silyl ketene acetal **8** (0.252 g, 1.21 mmol), and $BF_3 \cdot OEt_2$ (0.120 mL, 0.947 mmol). Analysis of the crude mixture revealed a 50:50 ratio of *cis*-**28** to *trans*-**28**. Purification by flash chromatography (20:80 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.175 g, 88%). Characterization matches reported values[36] and is reported for the isolated isomers *cis*-**28** and *trans*-**28**.

cis-**28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.17 (m, 8H), 7.07 (d, J = 7.9, 2H), 4.62−4.54 (m, 2H), 4.11 (d, J = 12.5, 1H), 3.92 (dddd, J = 10.4, 7.5, 5.3, 2.0, 1H), 3.54 (dd, J = 12.5, 1.2, 1H), 3.42 (br s, 1H), 2.86 (dd, J = 15.5, 7.9, 1H), 2.67 (dd, J = 15.5, 5.2, 1H), 2.12−2.06 (m, 1H), 1.86 (m, 1H), 1.71−1.63 (m, 1H), 1.62−1.55 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.0, 150.8, 138.8, 129.5, 128.5, 127.8, 127.7, 125.9, 121.8, 74.1, 70.4, 70.2, 69.7, 41.4, 27.0, 26.4; IR (thin film) 3066, 3031, 2944, 2858, 1756, 1594 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{22}NaO_4$ (M + Na)$^+$ 349.1416, found 349.1415.

trans-**28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40−7.19 (m, 8H), 7.08 (d, J = 7.7, 2H), 4.60 (d, J = 11.9, 1H), 4.54 (d, J = 11.9, 1H), 4.12 (ddd, J = 10.8, 4.7, 2.2, 1H), 3.84 (dddd, J = 10.6, 7.6, 5.2, 2.1, 1H), 3.49 (tt, J = 10.1, 4.5, 1H), 3.26 (t, J = 10.5, 1H), 2.74 (dd, J = 15.2, 7.9, 1H), 2.65 (dd, J = 15.2, 5.2, 1H), 2.27−2.19 (m, 1H), 1.92−1.84 (m, 1H), 1.57−1.40 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 150.8, 138.6, 129.6, 128.7, 127.9, 127.8, 126.1, 121.8, 74.2, 72.8, 71.0, 70.9, 41.1, 30.5, 30.1; IR (thin film) 3064, 3033, 2939, 2863, 1756, 1594 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{20}H_{22}NaO_4$ (M + Na)$^+$ 349.1416, found 349.1420. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.22; H, 6.80.

Methyl 2-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]-2-methyl-propanoate (29).[36] The standard procedure for nucleophilic substitution was followed with acetal **21** (0.101 g, 0.404 mmol), silyl ketene acetal **9** (0.295 g, 1.69 mmol), and $BF_3 \cdot OEt_2$ (0.080 mL,

0.64 mmol). Analysis of the crude mixture revealed a 58:42 ratio of *cis*-**29** to *trans*-**29**. Purification by flash chromatography (10:90 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.094 g, 80%). Characterization matches reported values[36] and is reported for the isolated isomers *cis*-**29** and *trans*-**29**.

cis-**29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.59 (d, J = 12.3, 1H), 4.51 (d, J = 12.3, 1H), 4.12 (d, J = 12.5, 1H), 3.68 (s, 3H), 3.55 (dd, J = 11.4, 1.7, 1H), 3.45 (dd, J = 12.5, 1.3, 1H), 3.38 (br s, 1H), 2.10 (dt, J = 13.9, 3.1, 1H), 1.81 (qd, J = 13.1, 3.7, 1H), 1.67−1.57 (m, 1H), 1.31 (br d, J = 12.8, 1H), 1.23 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.7, 139.1, 128.5, 127.64, 127.58, 82.4, 70.8, 69.9, 69.8, 52.0, 46.9, 27.8, 21.3, 20.64, 20.56; IR (neat) 2950, 2858, 1730, 1454, 1143, 1115 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{17}H_{24}NaO_4$ $(M + Na)^+$ 315.1572, found 315.1569. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.06; H, 8.32.

trans-**29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.57 (d, J = 12.0, 1H), 4.52 (d, J = 12.0, 1H), 4.09 (ddd, J = 10.7, 4.7, 2.3, 1H), 3.67 (s, 3H), 3.46−3.37 (m, 2H), 3.16 (t, J = 10.5, 1H), 2.26−2.18 (m, 1H), 1.66−1.60 (m, 1H), 1.50−1.34 (m, 2H), 1.16 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 138.8, 128.6, 127.9, 127.8, 82.3, 73.2, 71.3, 71.0, 52.1, 46.4, 30.3, 24.7, 21.7, 20.7; IR (neat) 2948, 2864, 1734, 1454, 1275, 1093 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{17}H_{24}NaO_4$ $(M + Na)^+$ 315.1572, found 315.1577. Anal. Calcd for $C_{17}H_{24}O_4$: C, 69.84; H, 8.27. Found: C, 70.00; H, 8.31.

Butyl 2-[5-(Benzyloxy)tetrahydro-2*H*-pyran-2-yl]acetate (30).[36] The standard procedure for nucleophilic substitution was followed with acetal **21** (0.105 g, 0.419 mmol), silyl ketene acetal **10** (0.156 g, 0.828 mmol), and $BF_3 \cdot OEt_2$ (0.080 mL, 0.64 mmol). Analysis of the crude mixture revealed a 60:40 ratio of *cis*-**30** to *trans*-**30**. Purification by flash chromatography (5:95 EtOAc/hexanes) afforded the product as a colorless, clear oil (0.110 g, 86%). Characterization matches reported values[36] and is reported for the isolated isomers *cis*-**30** and *trans*-**30**.

cis-**30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38−7.24 (m, 5H), 4.60−4.53 (m, 2H), 4.12−4.03 (m, 3H), 3.85−3.77 (m, 1H), 3.51 (dd, J = 12.5, 1.1, 1H), 3.40 (br s, 1H), 2.62 (dd, J = 15.5, 7.7, 1H), 2.41 (dd, J = 15.5, 5.4, 1H), 2.10−2.01 (m, 1H), 1.77 (qd, J = 13.2, 3.6, 1H), 1.69−1.57 (m, 3H), 1.51 (d, J = 12.0, 1H), 1.36 (sextet, J = 7.6, 2H), 0.92 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 138.8, 128.5, 127.7, 127.6, 74.2, 70.4, 70.1, 69.6, 64.5, 41.4, 30.8, 27.0, 26.4, 19.2, 13.9; IR (thin film) 2958, 2871, 1733, 1455, 1115 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{18}H_{26}NaO_4$ $(M + Na)^+$ 329.1729, found 329.1718. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.39; H, 8.48.

trans-**30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35−7.25 (m, 5H), 4.58 (d, J = 11.9, 1H), 4.52 (d, J = 11.8, 1H), 4.14−4.04 (m, 3H), 3.75−3.68 (m, 1H), 3.45 (tt, J = 10.0, 4.6, 1H), 3.21 (t, J = 10.5, 1H), 2.49 (dd, J = 15.1, 7.8, 1H), 2.39 (dd, J = 15.1, 5.2, 1H), 2.19 (br d, J = 12.4, 1H), 1.79 (br d, J = 12.9, 1H), 1.61 (quintet, J = 6.8, 2H), 1.54−1.44 (m, 1H), 1.42−1.32 (m, 3H), 0.92 (t, J = 7.5, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 138.6, 128.6, 127.9, 127.8, 74.2, 72.8, 71.0, 70.9, 64.6, 41.2, 30.8, 30.4, 30.1, 19.3, 13.9; IR (thin film) 2960, 2867, 1733, 1455, 1090 cm^{-1}; HRMS (TOF MS ES+) m/z calcd for $C_{18}H_{26}NaO_4$ $(M + Na)^+$ 329.1729, found 329.1720. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.49; H, 8.70.

Acknowledgment. This research was supported by the National Institutes of Health, National Institute of General Medical Sciences (Grant No. GM-61066 to K.A.W. and Grant No. 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 this 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: Complete experimental procedures, product characterization, stereochemical proofs, GC and spectral data, and references. This material is available free of charge via the Internet at http://pubs.acs.org.