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C-Glycosylation Reactions of Sulfur-Substituted Glycosyl Donors: Evidence against the Role of Neighboring-Group Participation

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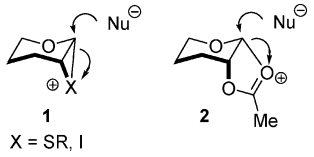
Abstract: Nucleophilic substitution reactions of C-4 sulfur-substituted tetrahydropyran acetals revealed that neighboring-group participation does not control product formation. Spectroscopic evidence for the formation of an intermediate sulfonium ion is provided, as are data from nucleophilic substitution reactions demonstrating that products are formed from oxocarbenium ion intermediates. The selectivity was not sensitive to solvent or to which Lewis acid was employed. The identity of the heteroatom at the C-4 position also did not significantly impact diastereoselectivity. Consequently, neighboring-group participation was not responsible for the formation of either the major or the minor products. These studies implicate a Curtin−Hammett kinetic scenario in which the formation of a low-energy intermediate does not necessitate its involvement in the product-forming pathway.

The use of neighboring-group participation to control stereochemistry has proven to be an effective strategy for a number of transformations.[1−6] Carbohydrate chemistry, in particular, has benefited from the application of anchimeric assistance in glycosylation reactions.[7,8] Sulfur-,[9,10] iodine-,[11,12] and acetoxy-substituted[5,13] glycosyl donors undergo highly trans-selective reactions, which have been postulated to involve nucleophilic ring-opening reactions (S_N2) of onium ion intermediates (Scheme 1).[14] For example, Boons and co-workers recently demonstrated the utility of neighboring-group participation in their elegant method for the synthesis of α-glycosides.[15] A protecting group containing a sulfur moiety was installed at the C-2 hydroxyl group, and upon activation, the derived sulfonium ion intermediate was observed spectroscopically.[15] The stereochemical outcome of subsequent nucleophilic substitution reactions was consistent with an S_N2 pathway involving this intermediate.[15,16]

Scheme 1. S_N2 Pathway Postulated to Account for Trans Product Formation



In this paper, we provide spectroscopic evidence for the formation of an analogous sulfonium ion intermediate in a tetrahydropyran system and demonstrate that the products are not formed by an S_N2 pathway. Instead, selectivity is the result of a Curtin−Hammett kinetic scenario[17] in which nucleophilic additions to high-energy oxocarbenium ion intermediates occur through overall lower energy pathways.[18] This analysis is consistent with previous experimental[19−21] and computational[22−24] studies demonstrating that the reactions of acetals bearing heteroatoms capable of neighboring-group participation might react through open cations. As was clearly demonstrated by Halpern's mechanistic studies of the asymmetric hydrogenation

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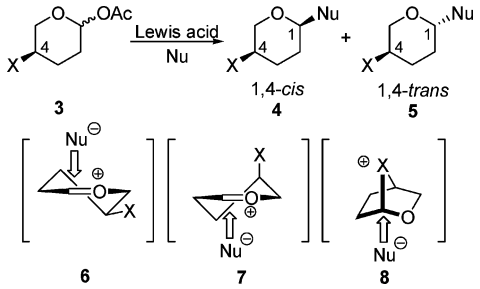
Scheme 2. Model System to Determine Mode of Stereocontrol

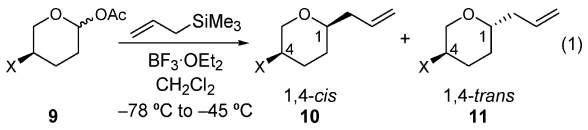


of olefins,[25] the fact that a low-energy intermediate can be structurally characterized does not establish that the intermediate is involved in product formation. For *C*-glycosylation reactions, it is clear that onium ion intermediates can be formed, but they need not be responsible for product formation.

To understand the role of neighboring-group participation involving sulfur-substituted glycosyl donors, a model system was designed to differentiate between stereoselective addition to an oxocarbenium ion and stereospecific ring-opening of a bridged intermediate. Nucleophilic substitution reactions of the 4-heteroatom-substituted acetal **3** would illuminate which of these pathways was preferred.[26] Activation of acetal **3** with a Lewis acid would give rise to a cation that could adopt three forms: the equatorial half-chair oxocarbenium ion **6**, the axial half-chair conformer **7**, and the bridged intermediate **8** resulting from heteroatom assistance. Nucleophilic addition to the stereoelectronically preferred face[27] of equatorial conformer **6** would afford the cis product **4**. Alternatively, addition to axial conformer **7** or ring-opening of sulfonium ion **8** with inversion would provide the trans product **5** (Scheme 2). Selective formation of the cis product **4**, therefore, would provide evidence against heteroatom assistance in the stereochemistry-determining step. Formation of the trans product **5** would require additional experiments to differentiate between the remaining two reaction pathways.

Details of the experimental design deserve mention prior to discussing the results of nucleophilic substitution reactions. In all cases, anomeric acetates were employed as oxocarbenium ion precursors.[28] Although the methyl acetals provided comparable diastereomeric ratios upon nucleophilic substitution, their reactions did not proceed to completion. Unless otherwise noted, allyltrimethylsilane was employed as the nucleophile to minimize steric destabilization upon nucleophile approach and because nucleophilic attack is irreversible.[29,30] Diastereomer ratios were obtained from unpurified reaction mixtures, and product stereochemistry was determined by analysis of both ^{1}H NMR coupling constant data and NOE measurements of the purified products.

Initial studies demonstrated that the major products of nucleophilic addition reactions to sulfur-substituted acetals **9a,b** (**3**, X = SEt, SPh) did not arise from an S_N2 pathway involving a sulfonium ion intermediate. Treatment of acetals **9** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ provided 1,4-*cis* products **10** preferentially (eq 1). The moderate cis-selectivity is consistent with previously published data on 4-iodine-substituted acetals, which indicated that iodonium ion **8** (X = I, Scheme 2) was not a reactive conformer.[26] The formation of cis products **10** demonstrated that sulfonium ions **8** (X = SR) could not be the reactive conformers in these reactions.[31] Instead, the major products arose from addition to equatorially substituted oxocarbenium ions **6** (X = SR).



compound	X	cis:trans	yield (%)
9a	SEt	84:16	75
9b	SPh	78:22	87
9c[26]	I	72:28	90

The reactions of acetals **9a**,**b** could lead to erroneous conclusions regarding the plausibility of nucleophilic substitution reactions via bridged intermediates. The proposed sulfonium ion arising from acetal **9** in the presence of a Lewis acid may be destabilized by the ring strain inherent to the [2.2.1] bridged bicyclic ring system.[32] Computational studies (B3LYP/6-31G*), however, indicate that sulfonium ion **14** is ≥5.5 kcal/mol lower in energy than oxocarbenium ions **12** and **13** (Figure 1).[33] This result is consistent with data regarding the greater stability of sulfonium ion intermediates as compared to their corresponding oxonium ions, although ring strain appears to attenuate this preference.[34−36] The calculated energies of the oxocarbenium ion intermediates (**12** and **13**), however, are not consistent with the diastereoselectivities observed in the reactions involving the addition of allyltrimethylsilane (eq 1). Either the sulfonium ion **14** was not formed, or it was not a direct precursor to the products.

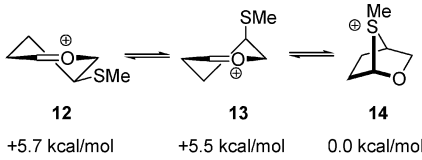


Figure 1. Calculated (B3LYP/6-31G*) enthalpies of 4-SMe-substituted oxocarbenium ion conformers.

Relieving the ring strain of the [2.2.1] ring system should provide access to a lower energy sulfonium ion intermediate,

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(28) Acetals **9**, **18**, and **24** were prepared from 3,4-dihydro-2-methoxypyran. Details of these syntheses are provided as Supporting Information.
(29) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.
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(31) Attempts to characterize an intermediate [2.2.1]-bridged bicyclic sulfonium ion **8** (X = SEt) by NMR spectroscopy were inconclusive.
(32) The analogous [2.2.1]-bridged carbocyclic ring system has a strain value of 14.4 kcal/mol: Wiberg, K. B. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 312−322.
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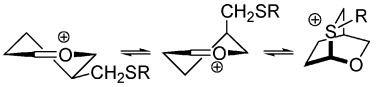
(34) Smith, B. J. *J. Phys. Chem. A* **1998**, *102*, 4728−4733.
(35) Smith (ref 34) demonstrated in a 1-SMe substituted pyran ring system that the protonated sulfonium ion form is favored enthalpically ($\Delta H°$) by 22 kcal/mol as compared to the dissociated oxocarbenium ion and methanethiol. Taking into account 14 kcal/mol ring strain for the [2.2.1] bicyclic system, the sulfonium ion **14** should be favored by 8 kcal/mol, in good agreement with computational results (Figure 1).
(36) Other strained sulfonium ions have previously been observed. See, for example: (a) Aggarwal, V. K.; Charmant, J.; Dudin, L.; Porcelloni, M.; Richardson, J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5467−5471. (b) Huang, X.; Batchelor, R. J.; Einstein, F. W. B.; Bennet, A. J. *J. Org. Chem.* **1994**, *59*, 7108−7116. (c) Wilder, P., Jr.; Feliu-Otero, L. A. *J. Org. Chem.* **1966**, *31*, 4264−4265.

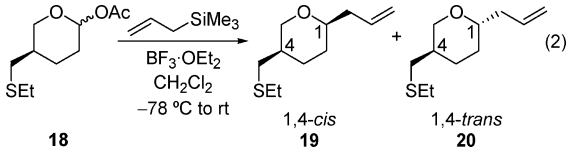


Compound	R	ΔH (kcal/mol)		
a	Me	+12.4	+14.4	0.0
b	Ph	+12.6	+13.5	0.0

Figure 2. Calculated (B3LYP/6-31G*) enthalpies of 4-CH_2SR-substituted oxocarbenium ion conformers.

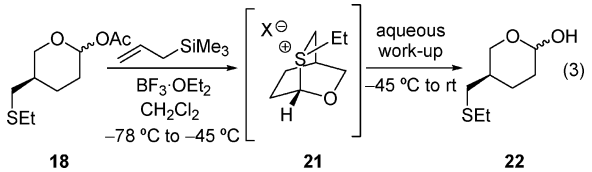
and, consequently, more product derived from this intermediate should be obtained. Extension of the sulfonium ion bridge of **14** by one methylene unit should alleviate ring strain. On the basis of the analysis of ring strain values of analogous carbocyclic systems, the [2.2.2]-bridged bicyclic sulfonium ion **17a** should be less strained by 7 kcal/mol as compared to the [2.2.1] system.[32] Calculations (B3LYP/6-31G*) support this hypothesis: the [2.2.2] bridged sulfonium ion **17a** was calculated to be 12.4 kcal/mol lower in energy than the equatorially substituted oxocarbenium ion half-chair conformer **15a** (Figure 2), and thus approximately 7 kcal/mol less strained than the [2.2.1]-bridged bicyclic sulfonium ion **14** (Figure 1).[33] Data for the thiophenyl-substituted cation show a similar preference for the bridged sulfonium ion **17b**.

Nucleophilic substitution reactions of acetate **18** indicate that the [2.2.2]-bicyclic sulfonium ion analogous to **17** is not the reactive conformer. Treatment of 4-CH_2SEt-substituted acetate **18** with allyltrimethylsilane and $BF_3{\cdot}OEt_2$ provided 1,4-*cis* product **19** as the major diastereomer upon warming to room temperature (eq 2). The cis product **19** could not arise from stereospecific ring-opening of sulfonium ion **17**. Instead, addition to the equatorially substituted oxocarbenium ion half-chair conformer **15** (R = Et) would provide the observed product.



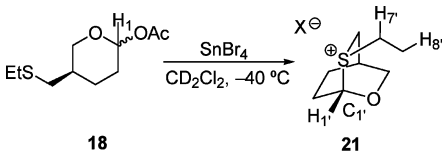
89:11 diastereoselectivity

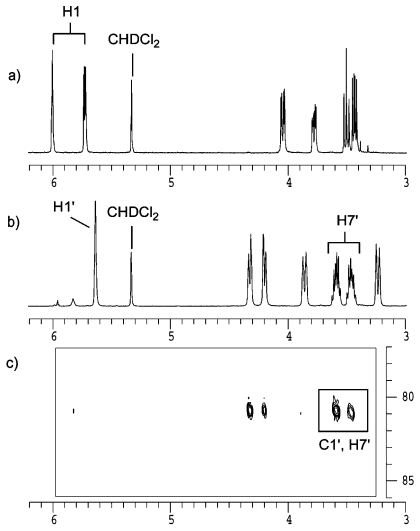
The higher temperature required to effect substitution of the 4-CH_2SEt-substituted acetate **18** as compared to the 4-SR-substituted acetals **9a**,**b** (eq 1) provides insight into the stability of sulfonium ion **21**. Allylation of acetate **18** did not proceed under the standard conditions employed for acetals **9a**,**b** (−45 °C); only hydrolysis products were isolated upon low-temperature quenching and aqueous workup (eq 3). We hypothesized that a stable sulfonium ion such as **21** was formed upon addition of $BF_3{\cdot}OEt_2$ to the reaction mixture. It was possible that sulfonium ion **21** would be unreactive toward allyltrimethylsilane.[21] Instead, nucleophilic addition could occur only upon opening of the stable sulfonium ion through the high-energy oxocarbenium ion conformers **15** and **16** (R = Et, Figure 2).[21]



Low-temperature NMR spectroscopy confirmed that the [2.2.2]-bridged bicyclic sulfonium ion **21** was formed upon

Scheme 3. Spectroscopic Evidence for the Formation of Sulfonium Ion **21**





Key: (a) ^{1}H NMR spectrum of acetate **18** (b) ^{1}H NMR spectrum of sulfonium ion **21** at –40 °C (c) HMBC spectrum of sulfonium ion **21**.

treatment of acetate **18** with Lewis acid. An anomeric mixture of acetate **18** was treated with $SnBr_4$ in CD_2Cl_2 at −40 °C (Scheme 3).[37] As described by Boons for an analogous system, an upfield shift of the anomeric protons (H1 to H1′) was observed, consistent with the formation of sulfonium ion **21**.[15] In addition, characteristic downfield shifts were observed for the protons adjacent to the sulfur atom, indicating the presence of an electron-withdrawing functionality on sulfur. Furthermore, irradiation of the bridgehead proton H1′ provided NOE correlations to the protons on the ethyl substituent (H7′ and H8′), demonstrating the proximity of the SEt group to H1′. An HMBC correlation between bridgehead carbon C1′ and H7′ indicated that the SEt group was connected to C1′. Although the bicyclic cation **21** was formed quantitatively at −40 °C, it did not appear to be a reactive intermediate, because nucleophilic substitution reactions with allyltrimethylsilane did not occur at this temperature (eq 3).

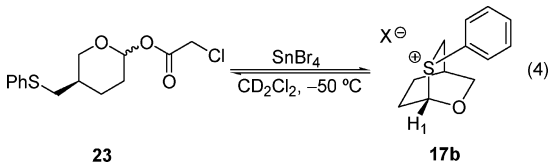
NMR spectroscopic data of the thiophenyl-substituted acetal are also consistent with the formation of a bridged sulfonium ion (**17b**, eq 4).[38] In contrast to the spectroscopic data obtained for the thioalkyl-substituted acetal **18**, a significant and reversible temperature dependence was observed upon the addition of $SnBr_4$ to chloroacetate **23** at −50 °C.[39] While nearly complete

(37) Employing PhSMe as the substrate under identical conditions indicated that the observed spectroscopic changes were not the result of complexation to the Lewis acid.

(38) In analogy to the characterization of sulfonium ion **21**, characteristic chemical shifts and NOE correlations indicated the formation of sulfonium ion **17b**. An HMBC correlation was not obtained in this system, however, presumably due to the fluctionality of the intermediate.

(39) Chloroacetate **23** was employed in spectroscopic studies because of its greater ability to ionize under Lewis acidic conditions. The acetate **24** also formed sulfonium ion **17b**, but the equilibrium significantly favored the starting acetate. Both chloroacetate **23** and acetate **24** afforded comparable product ratios upon subjection to standard allylation conditions.

conversion to sulfonium ion **17b** was observed at −80 °C, only a trace quantity of this species was observed at −20 °C. As depicted in eq 4, generation of sulfonium ion **17b** involves the formation of an ion pair[40,41] and the loss of one degree of rotation;[42] these changes would result in a negative entropy for the reaction ($\Delta S° < 0$).[43] An increase in temperature, therefore, would force the equilibrium toward the starting acetal.



(4)

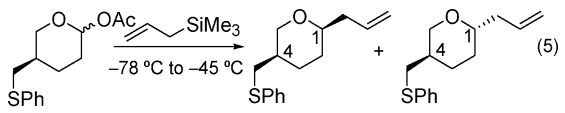
23 **17b**

Nucleophilic additions to 4-CH_2SPh-substituted acetate **24** also afforded the major diastereomer arising from addition to the equatorially substituted oxocarbenium ion **15b**. Treatment of 4-CH_2SPh-substituted acetate **24** with allyltrimethylsilane in the presence of BF_3·OEt_2 at −45 °C provided 1,4-*cis* **25** as the major product (eq 5). The selectivity of this reaction was not sensitive to solvent or to which Lewis acid was employed (Table 1). In all cases, the major product arose from nucleophilic addition to the stereoelectronically preferred face of the equatorially substituted oxocarbenium ion half-chair conformer **15b**, not the labile bicyclic cation **17b** that was observed spectroscopically (eq 4).

The difference in stability and reactivity between the 4-CH_2SEt- and 4-CH_2SPh-substituted cations is informative. Low-temperature NMR spectroscopy indicated that the thioalkyl-bridged sulfonium ion **21** was stable at all temperatures examined. Allylation, however, did not occur at −45 °C; instead, reactivity only occurred when the higher energy oxocarbenium ion conformers were formed rapidly upon warming to room temperature. In contrast, the thiophenyl-substituted acetal **24** formed the more labile sulfonium ion **17b**, as confirmed by variable-temperature NMR spectroscopy. Allylation occurred readily at −45 °C, albeit not through the intermediate sulfonium ion. These results suggest that the sulfonium ions observed in these systems are not reactive intermediates, but rather resting states that are transformed into oxocarbenium ion conformers and subsequently trapped by allyltrimethylsilane to afford the major products.

While the bicyclic sulfonium ion **17b** does not contribute to formation of the major product, an experiment was designed to explore whether this intermediate was responsible for the formation of the minor product. The 1,4-*trans* product **26** could be formed either by addition to the axially substituted oxocarbenium ion conformer **16b** or by ring-opening of sulfonium ion **17b** (Figure 2). To determine which of these processes was occurring, heteroatoms of varying donor ability were incorporated at the C-4 position. If the minor product arose from ring-opening of sulfonium ion **17b**, heteroatoms with greater donor ability would provide more of the 1,4-*trans* product **26**.[7] Because donor ability increases with nucleophilicity,[44] selenium-, sulfur-, and iodine-substituted acetals should provide the highest levels of 1,4-*trans* product **26**,[45] while substrates containing more electronegative heteroatoms (bromine, chlorine, or oxygen) would be less likely to form onium ions and should provide less trans product **26**.[7]

Table 1. Effect of Solvent and Lewis Acid on Allylation

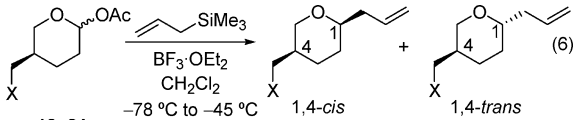


24 1,4-*cis* **25** 1,4-*trans* **26**

entry	Lewis acid	solvent	**25**:**26**[a]	yield (%)[b]
1	BF_3·OEt_2	CH_2Cl_2	87:13	89
2	BF_3·OEt_2	$CHCl_3$	86:14	77
3	BF_3·OEt_2	Et_2O	85:15	—[c]
4	BF_3·OEt_2	$C_6H_5CH_3$	84:16	74
5	$SnBr_4$	CH_2Cl_2	87:13	79
6	Me_3SiOTf	CH_2Cl_2	89:11	75
7	$EtAlCl_2$	CH_2Cl_2	87:13	80
8	$TiCl_4$	CH_2Cl_2	88:12	75

[a] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture. [b] Isolated yield. [c] GC analysis of the unpurified reaction mixture indicated minimal conversion to product.

Table 2. Effect of Heteroatom on Allylation



18, 24 1,4-*cis* **19, 25** 1,4-*trans* **20, 26**

entry	compound	X	cis:trans[a]	yield (%)[b]
1	**18**	SEt	89:11	87
2	**24a**	SPh	87:13	91
3	**24b**	SePh	91:9	92
4	**24c**	OPh	91:9	89
5	**24d**	Cl	92:8	90
6	**24e**	Br	92:8	85
7	**24f**	I	93:7	66
8	**24g**[c]	Bn	93:7	77

[a] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture. [b] Isolated yield. [c] See ref 26.

Products arising from neighboring-group participation were not the major products for any of the heteroatom-substituted acetals examined (eq 6, Table 2). Regardless of the type of heteroatom present, the allylated product 1,4-*cis* **25** predominated (eq 6, Table 2). The selectivities for strong donors (entries 1−3, 7) were comparable to those in which no heteroatom was present (entry 8).[26] Because no consistent correlation connects donor ability and diastereoselectivity, it can be concluded that neighboring-group participation does not significantly, if at all, contribute to formation of the minor product. Therefore, the product ratios obtained upon addition of allyltrimethylsilane are consistent with a scenario in which product formation arose from nucleophilic addition to the oxocarbenium ion half-chair conformers.

It is possible that a strong nucleophile is necessary to observe substitution through the sulfonium ion conformer. In glycosylation reactions where heteroatom assistance is utilized, alcohols are employed as the nucleophiles. According to Mayr's nucleo-

(40) Hayes, P. G.; Piers, W. E.; Parvez, M. *Organometallics* **2005**, *24*, 1173−1183.
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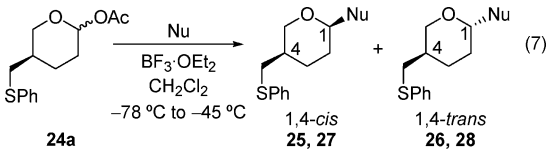
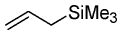
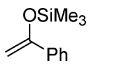
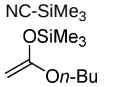
Table 3. Effects of Nucleophile on Selectivity



24a **25, 27** **26, 28**

entry	Nu	product	nucleophilicity parameter[a]	cis:trans[b]	yield (%)[c]
1		**25a/26a**	1.8	87:13	89
2		**27a/28a**	6.22	80:20	82
3	$NC\text{-}SiMe_3$	**27b/28b**	not defined	63:37	87
4		**27c/28c**	10.21	48:52	83

[a] See ref 46. [b] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture. [c] Isolated yield.

philicity parameters,[46] alcohols have a nucleophilicity value of $N \approx 6$.[47] Allyltrimethylsilane ($N = 1.8$) is less nucleophilic than an alcohol, so it may not be able to react by an S_N2 pathway through the bridged intermediate.[48]

Upon increasing nucleophilicity, selective formation of the 1,4-*trans* product **28** was not observed. Instead, stereoselectivity diminished as nucleophilicity increased (eq 7, Table 3).[49] Only a moderate loss of stereocontrol was observed for the addition of the acetophenone-derived silyl enol ether (entry 2), which has comparable nucleophilicity to an alcohol.[47] The stereocontrol was eroded further as the nucleophilicity was increased (entries 3 and 4). A similar trend has been reported for the nucleophilic substitution reactions of Me_3SiCN to oxocarbenium ions.[50] This loss of stereocontrol may be attributed to reactivity near the diffusion limit, in which both faces of each oxocarbenium ion conformer are available for nucleophilic addition. While the trend shown in Table 3 can be explained by considering oxocarbenium ions to be the reactive intermediates, it cannot be readily explained by consideration of stereospecific ring-opening of sulfonium ion **17b**.

The data presented in this paper demonstrate that sulfonium ions arising from 4-sulfur substituted acetals can be stable intermediates in nucleophilic substitution reactions to simple tetrahydropyran systems. Spectroscopic evidence confirmed the presence of these intermediates with varying stability depending on the nucleophilicity of the sulfur atom. The reactivity difference between thioalkyl- and thiophenyl-substituted acetals indicated that the sulfonium ion intermediates are not reactive intermediates, but that these intermediates open to form higher energy oxocarbenium ions. Nucleophilic addition to the preferred equatorially substituted oxocarbenium ion conformer is responsible for the stereoselectivity of the reaction.

The characterization of low-energy intermediates is a common practice for determining the source of stereochemical induction in a variety of reactions. The observation of stabilized intermediates, however, does not necessitate that the formation of the major products occur through these structures. It is important to consider all possible reactive intermediates before concluding which one must be responsible for product formation. This study affirms the importance of the Curtin−Hammett principle, which has been used successfully to explain the counterintuitive stereochemical outcomes for a number of reactions.[17]

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Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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