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Stereochemistry of Nucleophilic Substitution Reactions Depending upon Substituent: Evidence for Electrostatic Stabilization of Pseudoaxial Conformers of Oxocarbenium Ions by Heteroatom Substituents

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Abstract: Lewis acid-mediated nucleophilic substitution reactions of substituted tetrahydropyran acetates reveal that the conformational preferences of six-membered-ring cations depend significantly upon the electronic nature of the substituent. Nucleophilic substitutions of C-3 and C-4 alkyl-substituted tetrahydropyran acetates proceeded via pseudoequatorially substituted oxocarbenium ions, as would be expected by consideration of steric effects. Substitutions of C-3 and C-4 alkoxy-substituted tetrahydropyran acetates, however, proceeded via pseudoaxially oriented oxocarbenium ions. The unusual selectivities controlled by the alkoxy groups were demonstrated for a range of other heteroatom substituents, including nitrogen, fluorine, chlorine, and bromine. It is believed that the pseudoaxial conformation is preferred in the ground state of the cation because of an electrostatic attraction between the cationic carbon center of the oxocarbenium ion and the heteroatom substituent. This analysis is supported by the observation that selectivity diminishes down the halogen series, which is inconsistent with electron donation as might be expected during anchimeric assistance. The C-2 heteroatom-substituted systems gave moderately high 1,2-cis selectivity, while small alkyl substituents showed no selectivity. Only in the case of the *tert*-butyl group at C-2 was high 1,2-trans selectivity observed. These studies reinforce the idea that ground-state conformational effects need to be considered along with steric approach considerations.

Oxocarbenium ions are important reactive intermediates in both bioorganic[1−5] and synthetic organic chemistry.[6] For example, nucleophilic substitution reactions of cyclic acetals under acidic conditions likely proceed via oxocarbenium ion intermediates,[7] and these reactions provide methods for the synthesis of a number of important target structures.[8−12] The understanding of stereoselective reactions of oxocarbenium ions[13−15] requires consideration of the preferred conformation of the charged intermediate. Generally, the conformational preferences for charged intermediates are considered to be the same as those of neutral analogues such as tetrahydropyrans, with the caveat that the charged intermediates are flattened because of the trigonal atoms in the ring.[16]

In this paper, we report that the electronic nature of a substituent on a six-membered-ring oxocarbenium ion can exert a profound influence on the selectivity of its reactions with nucleophiles.[17] For example, we document that reactions involving cyclic oxocarbenium ions bearing electronegative substituents such as alkoxy groups often undergo reactions with opposite diastereoselectivities to those observed for alkyl-substituted cations.[18] While the reactions of alkyl-substituted cations appear to be governed by steric effects in the oxocarbenium ion, steric effects cannot explain the reactions of the heteroatom-substituted systems. The difference in selectivity can

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(18) We focused on comparisons between substituents at C-2, C-3, and C-4 because of difficulties associated with C-5 alkoxy-substituted systems. Placing an alkoxy group at C-5 of the cation would make a substrate with two acetal carbon centers, and the analysis would be complicated by the regioselectivity of oxocarbenium ion formation and isomerization of products. Pyran acetals with alkyl groups at C-5 normally undergo substitution with high anti selectivity. See, for example: Brown, D. S.; Ley, S. V.; Bruno, M. *Heterocycles* **1989**, *28*, 773−777.

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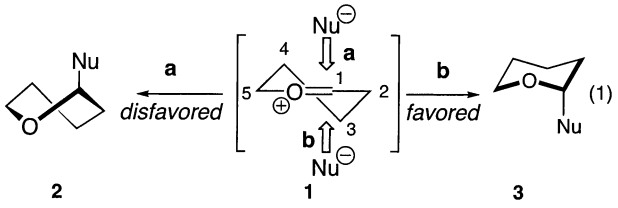
be attributed to the vastly different conformational preferences of carbocations relative to neutral systems. Our experiments suggest that heteroatom substituents adopt pseudoaxial positions in oxocarbenium ions because these orientations maximize attractive electrostatic interactions between the cationic carbon[19] and the partially negatively charged substituent.[20] Consequently, predictions of the conformational analysis of oxocarbenium ions (and likely iminium ions, vide infra) cannot be made based upon analogies to neutral species. In addition, conformational analysis of the oxocarbenium ion alone cannot account for selectivities observed in certain cases where developing destabilizing steric interactions in the transition state influence the course of the reaction.

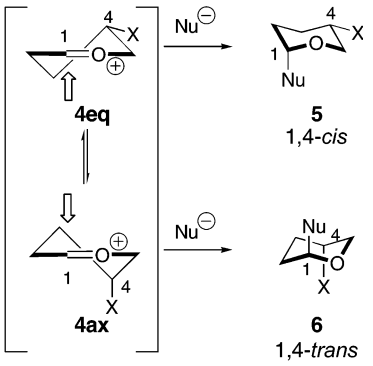
Background

The reactions of six-membered-ring oxocarbenium ions and iminium ions with nucleophiles can be understood by considering the ground-state conformation of the cation and the conformational changes that occur as it is transformed into the product. Tetrahydropyran oxocarbenium ion intermediates adopt half-chair conformations such as **1** (eq 1).[13−15] Nucleophilic attack on the cation occurs along a pseudoaxial trajectory to maximize overlap of the nucleophile HOMO with the LUMO of the oxocarbenium ion. For an oxocarbenium ion such as **1**, two potentially favorable modes of nucleophilic attack are possible (eq 1). Axial attack from the top face (a) of the oxocarbenium ion forms the product in the higher-energy twist-boat conformation (**2**). Nucleophilic addition along the axial trajectory from the bottom face (b) gives the lower-energy chair product (**3**). The chairlike pathway (b) is favored since it is expected to be formed by a lower-energy, chairlike transition state.[13−15]



When the oxocarbenium ion is substituted, such as C-4 alkyl-substituted oxocarbenium ion **4**, two diastereomeric half-chair conformers are possible (**4eq** and **4ax**, Scheme 1).[13−15] Steric effects are expected to favor pseudoequatorial conformer **4eq** rather than the more crowded pseudoaxial conformer **4ax**. According to the stereoelectronic preference for addition of nucleophiles through chairlike transition structures, the reaction of each conformer is expected to provide a different diastereomer of the product. In neither case are steric interactions developed between the C-4 substituent and the approaching nucleophile; therefore, the activation energies for reactions of **4eq** and **4ax** with a nucleophile should be comparable. Because nucleophilic attack should be slow relative to conformational interconversion,[21] the product ratio **5**:**6** should reflect the relative ground-state populations of **4eq** and **4ax**, as described by the Curtin−Hammett/Winstein−Holness concepts.[22,23]

Scheme 1



The influence of substitution at C-4 as shown in Scheme 1 represents a special case for six-membered-ring cations because external steric influences in the transition state are minimal. In general, the selectivities observed in the addition of nucleophiles to substituted oxocarbenium ions are determined by both the conformational preference of the intermediates and the reactivity of each conformer, as mandated by Curtin−Hammett/Winstein−Holness kinetics.[22,23] According to the Hammond Postulate,[24] the transition structures of these exergonic nucleophilic additions should be reactant-like.[25] As a result, factors that influence the stability of the oxocarbenium ion will also affect the energy of the transition state. In addition to ground-state influences, destabilizing steric interactions that develop in the transition state for nucleophilic addition may render one conformer less reactive than another. Consequently, the relative abundance of the different conformers of the cation and their relative reactivity (as determined by developing steric effects in the transition state) must both be considered. The C-4-substituted case is appealing because of its simplicity: the reactivity of the different conformers are equivalent since no differential steric interactions are developed; therefore, the product ratio should reflect the relative populations of the two conformers.[22,23]

Determination of the relative conformer populations of substituted oxocarbenium ions is not simple. The conformational preferences of alkyl-substituted six-membered-ring oxocarbenium ions can be evaluated similarly to neutral systems such as tetrahydropyrans and cyclohexanes.[13−15] In contrast, the preferences of heteroatom-substituted oxocarbenium ions do not necessarily follow the same pattern as their neutral counterparts. Bowen and co-workers reported molecular mechanics calculations suggesting that methyl substituents favor equatorial positions in oxocarbenium ions, while hydroxyl groups assume axial positions preferentially at certain positions (for example, eq 2).[16] The preference for hydroxyl groups to occupy axial positions was attributed to electrostatic forces that attract the partially negatively charged hydroxyl oxygen atom to the positively charged carbon atom.[19,26] The pseudoaxial conformers would be favored because the opposite charges are brought into closer proximity than in the equatorial conformers.[16] These conclusions were reinforced by ab initio calculations (RHF

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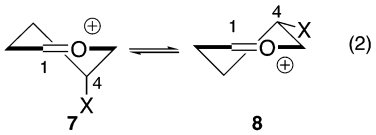
6-31G**) on C-4 alkoxy-substituted oxocarbenium ions reported by Miljkovic et al.,[27] who concluded that a through-space effect, but not anchimeric assistance (vide infra), stabilizes the axial conformation **7** (X = OMe) by about 4 kcal/mol relative to the equatorial conformer **8** (eq 2).[27]



X = OH, ΔG° = +4.7 kcal/mol
X = Me, ΔG° = –0.7 kcal/mol

The conclusions of Bowen[16] and Miljkovic[27] regarding the unusual conformers of heteroatom-substituted oxocarbenium ions suggested that these systems might exhibit unusual stereoselectivities upon reactions with nucleophiles. Several research groups have noted that their results are consistent with the reactions of oxocarbenium and iminium ions with pseudoaxial heteroatom substituents.[17,28−34] Oxocarbenium ions with pseudoaxial alkoxy groups have also been described for biologically relevant carbohydrate systems.[35,36] In other cases, the unusual conformational preferences of cations were not invoked. For example, reactions of six-membered-ring iminium ions substituted at C-4 with oxygen-containing groups provided high 1,4-trans selectivity comparable to our observations with oxocarbenium ions,[17] but these results were not explained at the time.[37,38]

In this paper, we detail our studies of the stereoselective reactions of six-membered-ring oxocarbenium ions.[17] A series of acetoxytetrahydropyrans were prepared and subjected to nucleophilic substitution reactions in the presence of Lewis acids, reactions which are believed to proceed via oxocarbenium ion intermediates.[7] These experiments illustrate the dramatic difference in diastereoselectivity between alkyl- and heteroatom-substituted systems. Studies with halogen-substituted acetals are consistent with the electrostatic argument proposed by Bowen[16] and Miljkovic.[27]

Results and Discussion

Details of the Experimental Approach. Several specific details of the experimental approach deserve comment:

1. The acetal substrates employed for this study were prepared, typically as mixtures of anomers, in several steps; the details of these syntheses are provided as Supporting Information.

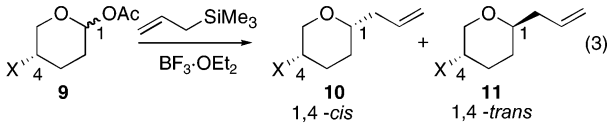
2. In all cases, studies were carried out using oxocarbenium ion precursors rather than iminium ion precursors, since the stereoselective reactions of iminium ions are frequently controlled by allylic strain.[39]

3. Anomeric acetates were employed as oxocarbenium ion precursors in all cases because the reactions proceeded in higher yields than if methoxy groups were employed. In several cases, substitution using methyl acetals showed selectivities that were comparable to the reactions with acetates. When a highly electron-withdrawing substituent such as a fluoro or nitro group was present, however, the reactions of the methyl acetals proceeded to provide ring-opened products instead.

4. Allyltrimethylsilane was generally employed as the nucleophile because the reactions are high-yielding and irreversible,[40] and the product cannot epimerize (as has been observed when silyl enol ethers,[28,41] oxygen nucleophiles,[42] or nitrogen nucleophiles are employed[43,44]). In addition, steric approach considerations are minimized with this small nucleophile,[45] and the allyl group can be manipulated easily to facilitate analysis of product stereochemistry.

5. The stereochemistry of the products was assigned by analysis of ^{1}H NMR coupling constants and NOE measurements on the products or their derivatives. These techniques provided reliable assignments because the 2-alkyltetrahydropyran products adopt chair conformers.[46]

Reactions of C-4 Substituted Tetrahydropyran Oxocarbenium Ions. A series of three experiments demonstrated that the computational studies of Bowen[16] and Miljkovic[27] (vide supra) could be employed to predict the stereoselective reactions of C-4 substituted oxocarbenium ions (eq 3). Acetals **9a−c** were treated with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane to provide allylated products **10** and **11**. Whereas the two alkyl-substituted systems **9a**,**b** provided preferentially the 1,4-cis products **10a**,**b**, the alkoxy-substituted acetal provided almost exclusively the 1,4-trans product **11c**. Similar selectivities were observed when $SnBr_4$ was employed as the Lewis acid. Because the methyl-substituted acetal **9a** and the phenethyl compound **9b** provided the same selectivity, it was concluded that the phenyl ring of the alkoxy group could not be the origin of the reversal of stereochemistry exhibited for **9c**.[41]



compound	X	cis : trans	yield (%)
a	Me	94 : 6	74
b	CH_2Bn	93 : 7	77
c	OBn	1 : 99	75

The selectivities of the nucleophilic substitution reactions of C-4 substituted six-membered-ring acetals (**9a−c**) can be

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(41) See, for example: Ichikawa, Y.-i.; Kubota, H.; Fujita, K.; Okauchi, T.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 845−852.
(42) For a recent example of equilibration during *O*-glycosylation, see: Chisholm, J. D.; Van Vranken, D. L. *J. Org. Chem.* **2000**, *65*, 7541−7553.
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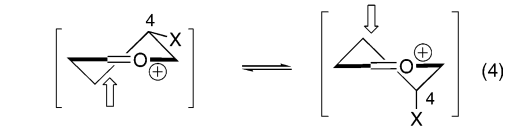
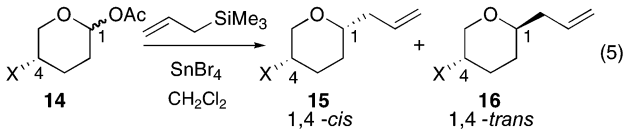
explained by analysis of the two possible half-chair conformers of the intermediate oxocarbenium ions **12** and **13** (eq 4). For the alkyl-substituted cations, the half-chair conformer **12**, with the substituent in the pseudoequatorial position, is likely preferred, as shown by Bowen (eq 2).[16] Addition of a nucleophile to this conformer would lead to the 1,4-cis product, in accord with the experimental results (eq 3) and the theory outlined in Scheme 1 (vide supra). Reaction through a pseudoequatorially substituted conformer, however, does not explain the behavior of the alkoxy-substituted system **9c**. If Bowen[16] and Miljkovic[27] are correct that an alkoxy group prefers to reside in a pseudoaxial position as in **13** (eq 4), then the fact that the 1,4-trans product predominates in this case can be easily understood. The analysis of the results with both alkyl- and alkoxy-substituted cations is also consistent with the notion that the C-4 substituents do not obstruct the approach of the incoming nucleophile, and conformational control dominates over steric approach control.



12 **13** (4)

The counterintuitive 1,4-trans selectivity exhibited by the benzyloxy-substituted oxocarbenium ion was also observed for other heteroatom-substituted systems (eq 5 and Table 1). When



14 **15** 1,4 -*cis* **16** 1,4 -*trans* (5)

Table 1. Influence of C-4 Substituent on Selectivity (eq 5)

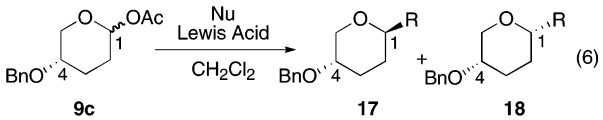
entry	compound	X	cis:trans[a]	yield (%)
1	**14a**	OSi*t*-BuPh$_2$	6:94	99
2	**14b**	OSO$_2$CH$_3$	4:96	76
3	**14c**	O$_2$C−C$_6$H$_5$	7:93	83
4	**14d**	O$_2$C−C$_6$H$_4$OCH$_3$	4:96	68
5	**14e**	O$_2$C−C$_6$H$_4$NO$_2$	19:81	87
6	**14f**	NO$_2$	15:85	91
7	**14g**	N$_3$	12:88	95

[a] Selectivities were determined by GC and confirmed by ^{1}H NMR spectroscopy.

the oxygen atom was functionalized as either a silyl ether, methanesulfonate ester, or benzoate ester, high 1,4-trans selectivities were observed (entries 1−3). The nature of the *para*-substituent on the benzoyloxy group, however, influenced the diastereoselectivity: whereas the *p*-methoxybenzoate **14d** showed higher selectivity than the benzoate **14c**, the *p*-nitrobenzoate **14e** exhibited lower selectivity (compare entries 3−5). Acetals bearing the nitrogen-containing groups NO$_2$ and N$_3$ showed 1,4-trans selectivities (entries 6 and 7) that were somewhat lower than those exhibited by the oxygen-containing groups.

The results shown in Table 1 suggest that all the oxocarbenium ions substituted at C-4 with an electronegative atom react through the same pseudoaxial conformer as expected[16,27] for the benzyloxy-substituted compound (vide supra). The preference for pseudoaxial conformers is consistent with the proposal[16,27] that an electrostatic attraction between the substituent and the oxocarbenium ion carbon[19,26] dictates the conformer population. This argument is also in accord with the trends exhibited by the benzoate substrates **14c**−**e**, which show that a decrease in electron density at the oxygen atom leads to a decrease in 1,4-trans selectivity (Table 1, entries 3−5). The fact that the nitrogen-containing substituents exhibit lower selectivity is also in agreement with an electrostatic argument,[16,27] since nitrogen is less electronegative than oxygen. It was surprising, however, to note that the reaction of the C-4 mesylate **14b** afforded such high 1,4-trans selectivity (96:4), considering that the methanesulfonyl group is a powerful electron-withdrawing group.[47] It is possible that the other two electron-rich oxygen atoms on the sulfur atom participate in the electrostatic stabilization of the pseudoaxially substituted oxocarbenium ion.

The high 1,4-trans selectivities for the allylations of heteroatom-substituted oxocarbenium ions were also observed for additions of other nucleophiles. Treatment of acetate **9c** with Et$_2$Zn in the presence of Me$_3$SiOTf[48] afforded a 98:2 mixture (trans:cis) of diastereomers **17a** and **18a** in 88% yield (eq 6). Addition of a silyl enol ether also proceeded with high diastereoselectivity (eq 6). The selectivity of addition of this nucleophile was only modestly influenced (±3%) by the nature of the Lewis acid (SnBr$_4$) and the solvent (toluene, EtCN, or EtNO$_2$).[49]



9c **17** 1,4 -*trans* **18** 1,4 -*cis* (6)

Compound	Nu	Lewis Acid	R	*trans* : *cis*[a]	yield (%)
a	Et$_2$Zn	Me$_3$SiOTf	Et	98 : 2	88
b		BF$_3$·OEt$_2$	CH$_2$COPh	93 : 7	74

[a] Selectivities were determined by GC and confirmed by ^{1}H NMR spectroscopy.

Investigations into the Nature of the Interaction between an Oxocarbenium Ion and an Axial Electronegative Substituent on the Ring. Two competing arguments can be forwarded to explain the 1,4-trans selectivity exhibited by heteroatom-substituted oxocarbenium ions. Bowen and Miljkovic[16,27] conclude that an electrostatic attraction between the electronegative substituent and the positive charge of the oxocarbenium, which resides on the carbon atom,[19,26] stabilizes

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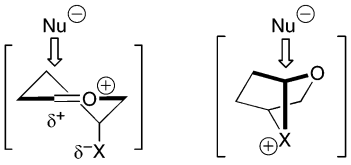
(48) Powell, N. A.; Rychnovsky, S. D. *J. Org. Chem.* **1999**, *64*, 2026−2037 and references therein.
(49) In some cases, solvent can dramatically alter the stereochemical outcomes of substitution reactions involving pyran acetals. See, for example: (a) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430−2434. (b) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882.

the pseudoaxial conformer **19**. Stereoelectronic effects[13,14] (vide supra) dictate that the 1,4-trans isomer would be formed from this cation. Alternatively, anchimeric assistance to form a bridged bicyclic system as shown in **20** would also lead to the same selectivity. While Miljkovic's computational data suggested that the bridged structure was not a minimum energy structure,[27] experimental evidence eliminating this possibility was desirable.

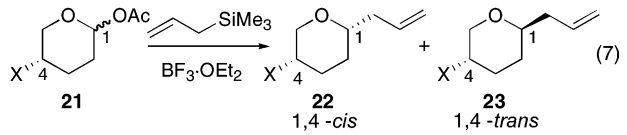


19 **20**

An experiment was designed employing a series of C-4 halogen-substituted oxocarbenium ions to place the two hypotheses in competition. Because electronegativity decreases down the halogen series F (4.0) > Cl (3.0) > Br (2.8) > I (2.5),[50] the C−X covalent bond becomes less polarized down the series, leading to a lower partial negative charge on the substituent. In addition, the carbon−halogen bond length increases along the series F (1.40 Å) < Cl (1.79 Å) < Br (1.97 Å) < I (2.16 Å),[50] which moves the two charges further apart and reduces electrostatic interactions. Consequently, if a through-space electrostatic interaction were occurring (as in **19**), 1,4-trans selectivity would decrease down the series: F > Cl > Br > I.

On the other hand, if anchimeric assistance (a through-space electron donation) controlled the selectivity, as shown in **20**, the trend for the halogens would be the opposite. Because the nucleophilicity of the halogen lone pairs increases down the halogen series F < Cl < Br < I, bromine and iodine would most effectively stabilize bridged intermediate **20**. This argument explains why bromonium ions are stable (even isolable[51]), whereas fluoronium ions are much higher in energy than acyclic 2-fluoroalkyl cations.[52] If nucleophilic substitution proceeded through bridged cation **20**, the iodo- and bromo-substituted tetrahydropyran acetals should undergo substitution with higher trans selectivity than the chloro- and fluoro-substituted analogues.

The selectivities observed for the halogen series **21a**−**d** (eq 7, Table 2) are in accord with the proposed electrostatic model (**19**) and discount the anchimeric assistance model (**20**). Allylation of the C-4 fluoro-substituted acetate **21a** resulted in the highest 1,4-trans selectivities (96:4) of the halogen series. This observation could have significance in bioorganic and medicinal chemistry because the replacement of hydrogen atoms with fluorine atoms is a common practice in these disciplines.[53−55] Evidently, this simple replacement can have a profound influence on conformations of charged intermediates. The chloro- and bromo-substituted analogues **21b** and **21c** gave progressively lower selectivities.[56] Nucleophilic substitution of the C-4



21 **22** 1,4 -*cis* **23** 1,4 -*trans*

Table 2. Influence of C-4 Halogen on Selectivity (eq 7)

entry	compound	X	cis:trans[a]	yield (%)
1	**21a**	F	4:96	45[b]
2	**21b**	Cl	14:86	90
3	**21c**	Br	29:71	87
4	**21d**	I	72:28	90

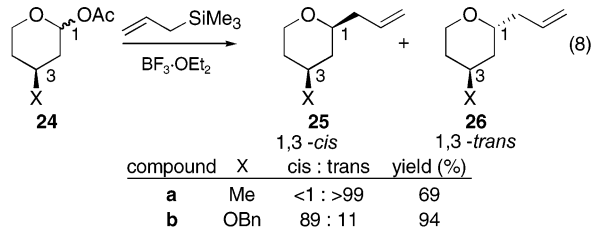
[a] Selectivities were determined by GC and confirmed by ^{1}H NMR spectroscopy. [b] Because of the high volatility of the allylated products, this reaction was monitored by ^{1}H NMR sepctroscopy, and the yield refers to the corresponding primary alcohol obtained upon hydroboration/oxidation. Details are provided as Supporting Information.

iodo-substituted acetate with allyltrimethylsilane provided the 1,4-cis product **22d**, which represents the same facial selectivity as an alkyl substituent (eq 3). This trend in selectivity is consistent with preliminary ab initio calculations, indicating that the preference for the pseudoaxial conformer **19** decreases along the series F > Cl > Br, with the iodo-substituted oxocarbenium ion preferring a pseudoequatorial position.

Reactions of C-3 Substituted Tetrahydropyran Oxocarbenium Ions. The results with C-4 substituted oxocarbenium ions suggested that electrostatic effects would also be important in the reactions of C-3 substituted oxocarbenium ions. Analogous to observations with the C-4 substituted systems, Bowen reported that C-3 alkyl-substituted oxocarbenium ions favored pseudoequatorial conformers and C-3 alkoxy-substituted cations prefer pseudoaxial conformers.[16] Considering the successful correlation of computational predictions[16,27] with the experimental results described in eq 3 and Table 1, reactions proceeding via C-3 substituted cations were investigated.

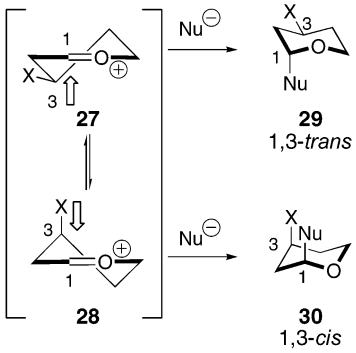
As was observed in the C-4 systems, reactions of oxocarbenium ions substituted at C-3 with alkyl or alkoxy groups demonstrate divergent diastereoselectivity. Nucleophilic substitution on methyl-substituted acetal **24a** provided the 1,3-trans product **26a** with high selectivity,[57] and the benzyloxy-substituted analogue **24b** provided 1,3-cis product **25b** with high selectivity (eq 8). The results can be explained by considering that a C-3 methyl-substituted cation favors the pseudoequatorial conformer **27**,[16] while a benzyloxy-substituted cation prefers the pseudoaxial conformer **28** because of an electrostatic attraction between the cationic carbon[19,26] and the heteroatom substituent (Scheme 2).[16] The formation of major product **25b** also provides another argument against anchimeric assistance in the reactions of heteroatom-substituted oxocarbenium ions. If anchimeric assistance were occurring, then the 1,3-trans product would predominate for acetate **24b**.

(50) Smith, M. B.; March, J. *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*; 5th ed.; Wiley: New York, 2001; pp 14 and 20.
(51) Slebocka-Tilk, H.; Ball, R. G.; Brown, R. S. *J. Am. Chem. Soc.* **1985**, *107*, 4504−4508.
(52) Hehre, W. J.; Hiberty, P. C. *J. Am. Chem. Soc.* **1974**, *96*, 2665−2677.
(53) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: New York, 1993.
(54) Carbon−fluorine bonds in small molecule enzyme inhibitors appear to be involved in attractive contacts with carbonyl groups of peptides: Olsen, J. A.; Banner, D. W.; Seiler, P.; Obst Sander, U.; D'Arcy, A.; Stihle, M.; Muller, K.; Diederich, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 2507−2511.
(55) Fluorine substituents can alter the conformations of peptides. See: Hodges, J. A.; Raines, R. T. *J. Am. Chem. Soc.* **2003**, *125*, 9262−9263 and references therein.
(56) Evidence that these reactions proceeded by oxocarbenium ions was provided by the acetates **21b**. In this case, the two anomers of the starting material were separable, and both anomers give the same product with the same degree of selectivity.
(57) The preference for 1,3-cis selectivity with alkoxy-substituted oxocarbenium ions is outweighed by 1,5-selectivity with alkyl groups: Keck, G. E.; Lundquist, G. D. *J. Org. Chem.* **1999**, *64*, 4482−4491.



compound	X	cis : trans	yield (%)
a	Me	<1 : >99	69
b	OBn	89 : 11	94

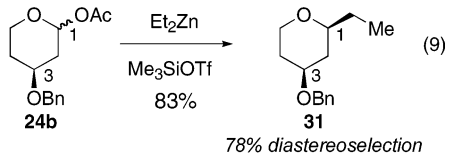
Scheme 2



Careful examination of Scheme 2 reveals that the analyses of reactions of C-3 substituted oxocarbenium ions are more complicated than for their C-4 substituted analogues. Unlike the C-4 substituted systems, the pseudoaxial substituent at C-3 of cation **28** is in a position to inhibit approach of the nucleophile to the electrophilic carbon atom. As a result, the rate of nucleophilic attack on the axial conformer **28** should be lower than for attack on the equatorial conformer **27** (that is, the pseudoaxial conformer **28** is less reactive than the pseudoequatorial one). The necessity to consider the relative reactivities of different conformers of a reactive species is a central element of the Curtin−Hammett kinetic scenario.[22,23]

While consideration of ground-state structures correctly predicts the sense of diastereoselectivity shown in eq 8, the magnitude of the selectivity depends on the developing destabilizing interactions in the transition state. Preferential formation of the 1,3-cis product **25b** indicates that the benzyloxy substituent is not large enough to force the reaction to occur via the less stable pseudoequatorial conformer **27** (X = OBn). This result can be understood because the developing 1,3-diaxial interaction (a *syn*-pentane-like orientation between an oxygen group and an alkyl group) is only a fraction of what it would be if both substituents were alkyl groups.[58] On the other hand, the excellent 1,3-trans selectivity (>99:1) obtained with **24a** is not fully accounted for by the moderate pseudoequatorial preference (1.3 kcal/mol) of the C-3 methyl-substituted oxocarbenium ion **27** (X = Me).[16] Although the pseudoaxial conformer **28** (X = Me) is likely to be present to a small extent, it is less reactive, since nucleophilic attack on this conformer would develop a destabilizing *syn*-pentane interaction.[59]

The importance of destabilizing interactions in the transition state was emphasized by reaction of the benzyloxy-substituted cation with another nucleophile. If ground-state effects were the only important influence on selectivity, then selectivities with all nucleophiles should be comparable. Nucleophilic substitution with Et_2Zn, however, resulted in a diminished 1,3-cis selectivity (78:22, eq 9) as compared with the reaction using allyltrimethylsilane as the nucleophile (89:11). The reduced selectivity may indicate that Et_2Zn is a larger nucleophile than allyltrimethylsilane, and developing steric interactions with the C-3 substituent play a larger role in controlling the selectivity. We have documented that the size of the nucleophile can even reverse selectivity in related systems.[45,60,61]



Reactions of C-2 Substituted Tetrahydropyran Oxocarbenium Ions. The results with the C-3 substituted oxocarbenium ions stress the importance of considering both ground-state and transition-state effects when analyzing stereoselective reactions, as required by careful application of the Curtin−Hammett/Winstein−Holness concepts.[22,23] The potential for competition between these effects is illustrated clearly by studies of C-2 substituted oxocarbenium ions.

Allylation of C-2 substituted tetrahydropyran acetals proceeded with little selectivity if either a methyl or isopropyl group were present at this position, but a benzyloxy group led to 1,2-cis selectivity (eq 10 and Table 3, entries 1−3). The enhanced

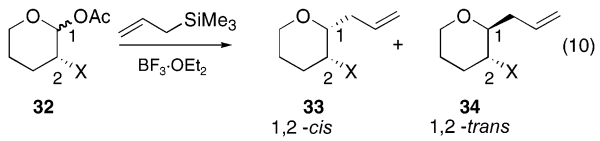


Table 3. Lewis Acid-Facilitated Allylations of **32a**−**d** (eq 10)

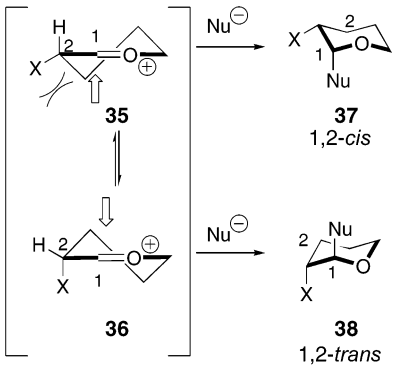
entry	compound	X	cis:trans[a]	yield (%)
1	**a**	OBn	83:17	85
2	**b**	Me	52:48	57
3	**c**	*i*-Pr	40:60	44
4	**d**	*t*-Bu	1:99	58

[a] Selectivities were determined by GC and confirmed by ^{1}H NMR spectroscopy.

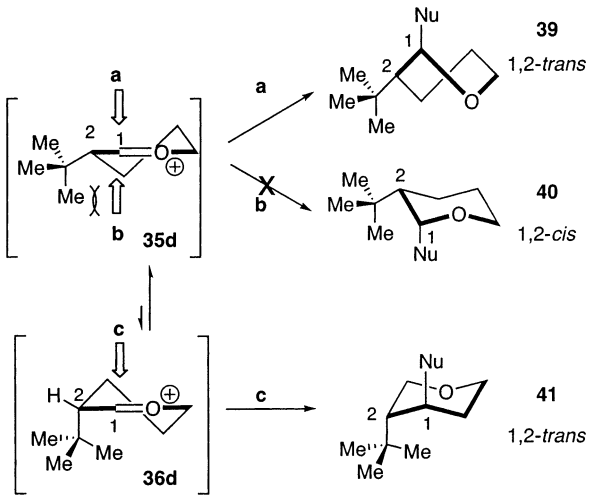
selectivity of the alkoxy group is the result of both ground-state and transition-state effects (Scheme 3). Bowen showed that while both C-2 alkyl and alkoxy groups prefer pseudoequatorial orientations in the oxocarbenium ions **35**, the conformational bias of the sterically smaller alkoxy group is higher (1.5 kcal/mol) than for the methyl group (0.8 kcal/mol).[16] The enhanced preference for the alkoxy group to occupy a pseudoequatorial position (as in **35**) may be understood by considering orbital effects. Because σ_{C-H} is a more effective donor than σ_{C-O},[62] hyperconjugation between the electron-donating pseudoaxial C−H bond at C-2 and the adjacent 2*p* orbital on the carbocationic carbon atom stabilizes the pseudoequatorial conformer, but no such stabilization is possible for the pseudoaxial conformer **36**. Transition-state arguments are also consistent with the selectivity. Developing gauche interactions

(58) Ohno, K.; Yoshida, H.; Watanabe, H.; Fujita, T.; Matsuura, H. *J. Phys. Chem.* **1994**, *98*, 6924−6930.
(59) Wiberg, K. B.; Murcko, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8029−8038.
(60) Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **1997**, *62*, 6706−6707.
(61) Shaw, J. T.; Woerpel, K. A. *Tetrahedron* **1999**, *55*, 8747−8756.
(62) Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910−3919.

Scheme 3



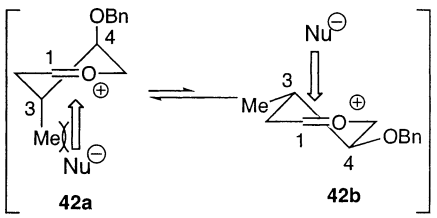
Scheme 4



between the nucleophile and the benzyloxy substituent at C-2 should be less than half what they would be for the C-2 methyl substituent in **35** based upon the A-value of methoxycyclohexane.[63] Because hindrance to steric approach is minimal, the nucleophile can approach from the same face as the adjacent benzyloxy substituent to provide predominantly the 1,2-cis product **37** (Scheme 3). In the case of the alkyl substituent at C-2, the minimal preference for the pseudoequatorial conformer **35** and the developing destabilizing interactions in the transition state oppose each other, leading to low selectivity.

When an extremely large alkyl substituent is present at C-2, the stereoselectivities are high. Allylation of the *tert*-butyl substituted acetate **32d** provided the product with high 1,2-trans selectivity (Table 3, entry 4). This stereochemical outcome is inconsistent with the most straightforward analysis. The *tert*-butyl group should adopt a pseudoequatorial position in the oxocarbenium ion,[64] and nucleophilic attack should occur along an axial trajectory through a chairlike transition state (Scheme 4, pathway b). The product resulting from this attack, however, would be the 1,2-cis product **40**, which was not observed. Pathway b is disfavored by a developing *syn*-pentane interaction[59] between the nucleophile and one of the methyl groups of the *tert*-butyl group. While nucleophilic attack could occur through the high-energy pseudoaxial conformer **36d** to provide the 1,2-trans product **41**, this possibility is unlikely, because *tert*-butyl groups experience severe destabilizations in axial positions.[64] A more satisfying explanation for the observed trans relationship is axial attack on the pseudoequatorial oxocarbenium ion (pathway a, Scheme 4) to provide the twist product **39**. While the twist conformer is not generally considered a low-energy conformer, for *tert*-butylcyclohexane it is lower in energy than the axially substituted conformer resembling **41**.[64] This example represents an exception to the commonly accepted stereoelectronic model for attack on six-membered-ring cations, which typically proceed via chairlike transition structures.[13−15]

Disubstituted Systems. While the experiments described here have focused on the influence of a single substituent on selectivity, oxocarbenium ions with several substituents should react with selectivities resulting from the aggregated influences of the substituents.[57] An experiment was designed to measure the relative importance of the conformational preference of the oxocarbenium ion (the ground-state effect) and destabilizing steric interactions that emerge upon approach of the nucleophile (the transition-state effect). The disubstituted oxocarbenium ion **42** would be expected to adopt two different conformers that would lead to opposite stereoselectivities (eq 11). An estimate of the relative energies of the two conformers can be made using the preferences for substituents at the individual positions, because gauche interactions between the alkyl and alkoxy substituents would be minimal in the diequatorial conformer **42b**.[58,63] According to Bowen,[16] the electrostatic stabilization imparted by the pseudoaxial C-4 benzyloxy substituent (4.7 kcal/mol) of **42a** would override the pseudoequatorial preference of the C-3 methyl substituent (0.7 kcal/mol), making diaxial oxocarbenium ion conformer **42a** lower in energy by approximately 4 kcal/mol. These two conformers, however, should react at different rates.[22,23] The trajectory of nucleophilic attack over the pseudoaxial C-3 methyl substituent should attenuate the reactivity of the lower-energy diaxial conformer **42a** (vide supra, eq 8). Alternatively, diequatorial conformer **42b** is predicted to be higher in energy but potentially more reactive because of the lack of steric interactions between the C-3 substituent and the incoming nucleophile.

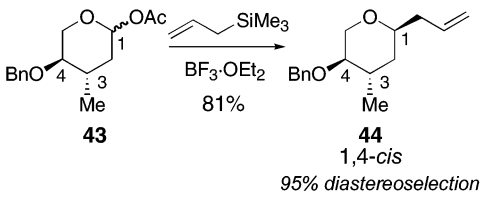


(11)

The experiment shows that for the cation **42**, steric interactions in the transition state appear to be more important than electrostatic interactions in the ground state. Treatment of the disubstituted acetate **43** with allyltrimethylsilane in the presence of a Lewis acid resulted in the selective formation of the 1,4-cis product **44** (eq 12). This product arises from attack of the nucleophile on the diequatorial oxocarbenium ion conformer **42b** (eq 11), which is likely to be the higher-energy conformer (vide supra). This type of stereochemical control is consistent with Curtin−Hammett kinetics:[22,23] because the two oxocarbenium ion conformers are in rapid equilibrium, destabilizing interactions in the transition state cause the lower-energy diaxial

(63) For a detailed discussion of the conformations of di- and polysubstituted six-membered-ring compounds, see: Eliel, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; Wiley: New York, 1994; pp 700−709.
(64) Manoharan, M.; Eliel, E. L. *Tetrahedron Lett.* **1984**, *25*, 3267−3268.

conformer **42a** to react considerably slower than the higher-energy conformer **42b**.



43 **44** 1,4-*cis* *95% diastereoselection*

Conclusion

The conformational preferences of six-membered-ring cations cannot be predicted by simply considering the conformational biases of neutral systems. The sense of stereoselectivity of nucleophilic addition to six-membered-ring oxocarbenium ions depends significantly upon the electronic nature and position of the substituent. Transition-state effects can play a large role depending upon the substitution pattern. Reactions of oxocarbenium ions substituted at C-4 are governed by ground-state conformational preferences, since no destabilizing steric effects develop in the transition state for nucleophilic attack. Alkyl groups adopt pseudoequatorial positions, leading to 1,4-cis selectivity, whereas oxygen-containing substituents such as alkoxy and acyloxy groups prefer pseudoaxial positions, resulting in 1,4-trans selectivity. Experiments with halogen-substituted acetals suggest that this selectivity is due to the electrostatic stabilization of the oxocarbenium ion by the partially negatively charged substituent.[16,27] An alkoxy substituent at C-3 of the oxocarbenium ion also stabilizes the pseudoaxial conformer, leading to the 1,3-cis product. The selectivities in C-3 substituted cases, however, are modulated by destabilizing steric interactions that arise in the transition state for nucleophilic attack. Nucleophilic additions to C-2 substituted oxocarbenium ions are also influenced by transition-state effects, explaining why methyl- and isopropyl-substituted cations give lower selectivity than the alkoxy-substituted systems. In the case of a *tert*-butyl group at C-2, high 1,2-trans selectivity is likely the result of a stereoelectronically disfavored reaction via a twistlike transition structure.

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Supporting Information Available: Complete experimental procedures, product characterization, and stereochemical proofs (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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