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Nucleophilic Additions of Trimethylsilyl Cyanide to Cyclic Oxocarbenium Ions: Evidence for the Loss of Stereoselectivity at the Limits of Diffusion Control

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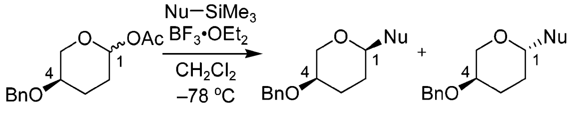
Abstract: The limitations of stereoelectronic models in assessing the stereoselective nucleophilic substitution reactions of cyclic oxocarbenium ions at high reaction rates are discussed. Evidence is provided suggesting that the diastereoselectivity of nucleophilic substitution reactions is attenuated at the limits of diffusion control. The low diastereoselectivities observed in the reactions of trimethylsilyl cyanide with five- and six-membered ring oxocarbenium ions are attributed to the high reactivity of the nucleophile and its reactions with these electrophiles at diffusion control rates.

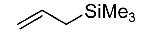
Introduction

Stereoelectronic models that explain the course of the nucleophilic substitution reactions of cyclic oxocarbenium and iminium ions have emerged as powerful tools in synthetic organic chemistry.[1−6] Although these models are frequently employed in the planning of syntheses,[7−11] product stereoselectivities occasionally do not conform to predictions.[12−15] For example, the stereoelectronic model used to rationalize the 1,4-trans diastereoselectivity in the reaction of acetal **1** with allyltrimethylsilane cannot account for the low diastereoselectivity observed for the reaction of **1** with trimethylsilyl cyanide (Me_3SiCN, eq 1).[16] Knowledge of the circumstances under which stereoelectronic models fail to make accurate stereochemical predictions would not only define the limitations of these models but also provide strategies to modify a reaction to ensure the desired stereochemical outcome.



(1)

1 1,4-cis **2a** 1,4-trans **2b**

Nu−SiMe$_3$	**2a** : **2b**[a]	yield (%)[b]
SiMe$_3$	4 : 96	90
N≡C−SiMe$_3$	32 : 68	76

[a]Measured by GC analysis of unpurified reaction mixture. [b]Based on purified products.

In this paper, we provided evidence suggesting that the modest diastereoselectivity observed in the reaction of Me_3SiCN with cyclic oxocarbenium ions (such as in eq 1) can be attributed to the high reactivity of the nucleophilic species involved.[17] The data are consistent with the formation of an anionic siliconate that delivers a cyano group to the highly electrophilic oxocarbenium ion[18,19] at the diffusion control limit (10^9−10^{10} $M^{-1}s^{-1}$).[20,21] At the diffusion control limit, nucleophilic addition to both diastereotopic faces of a cationic intermediate will lead to product formation because every collision between reactants leads to product.[22] Because the facial selectivity is determined by the encounter of the nucleophile and the electrophile, stereoelectronic effects cannot operate. The loss of stereoselectivity at the diffusion rate limit is predicated upon the work of Mayr, who has examined the reactions of ambident nucleophiles with cationic electrophiles.[23−25] The regioselectivities of

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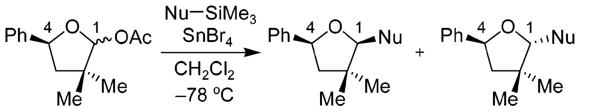
(1) Stevens, R. V.; Lee, A. W. M. *J. Am. Chem. Soc.* **1979**, *101*, 7032−7035.
(2) Stevens, R. V. *Acc. Chem. Res.* **1984**, *17*, 289−296.
(3) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983; pp 209−221.
(4) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 1169−1174.
(5) Schmitt, A.; Reissig, H.-U. *Eur. J. Org. Chem.* **2000**, 3893−3901.
(6) Bur, S. K.; Martin, S. F. *Org. Lett.* **2000**, *2*, 3445−3447.
(7) Yu, X. M.; Han, H. J.; Blagg, B. S. J. *J. Org. Chem.* **2005**, *70*, 5599−5605.
(8) Ghosh, S. K.; Hsung, R. P.; Liu, J. *J. Am. Chem. Soc.* **2005**, *127*, 8260−8261.
(9) Sohn, J.-H.; Waizumi, N.; Zhong, H. M.; Rawal, V. H. *J. Am. Chem. Soc.* **2005**, *127*, 7290−7291.
(10) Berry, C. R.; Hsung, R. P.; Antoline, J. E.; Petersen, M. E.; Challeppan, R.; Nielson, J. A. *J. Org. Chem.* **2005**, *70*, 4038−4042.
(11) Colby, E. A.; O'Brien, K. C.; Jamison, T. F. *J. Am. Chem. Soc.* **2005**, *127*, 4297−4307.
(12) Utimoto, K.; Wakabayashi, Y.; Horiie, T.; Inoue, M.; Shishiyama, Y.; Obayashi, M.; Nozaki, H. *Tetrahedron* **1983**, *39*, 967−973.
(13) Brown, D. S.; Bruno, M.; Davenport, R. J.; Ley, S. V. *Tetrahedron* **1989**, *45*, 4293−4308.
(14) Minehan, T. G.; Kishi, Y. *Tetrahedron Lett.* **1997**, *38*, 6815−6818.
(15) Lai, W.; Martin, O. R. *Carbohydr. Res.* **1993**, *250*, 185−193.
(16) The numbering used in this paper considers the carbocationic carbon as C-1
(17) For examples of other nonstereoselective additions of trimethylsilylcyanide to oxocarbenium ions, see: (a) Rychnovsky, S. D.; Dahanukar, V. H. *J. Org. Chem.* **1996**, *61*, 7648−7649. (b) de las Heras, F. G.; Fernandez-Resa, P. *J. Chem. Soc., Perkin Trans. 1* **1982**, 903−907.
(18) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *34*, 981−988.
(19) Amyes, T. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900.
(20) Bartl, J.; Steenken, S.; Mayr, H.; McClelland, R. A. *J. Am. Chem. Soc.* **1990**, *112*, 6918−6928.
(21) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66−77.
(22) A similar situation can also arise if nucleophilic addition to one diastereotopic face of a cationic intermediate proceeds at the diffusion control rate, whereas addition to the other face does not.

10.1021/ja061110u CCC: $33.50

these reactions do not adhere to conventional models used to rationalize the reactivity of ambident nucleophiles[26] because they occur at the diffusion rate limit. Similarly, the stereoelectronic models employed to predict the course of nucleophilic substitution reactions of cyclic acetals in organic media will also fail when assessing reactions proceeding at or near the rate of diffusion.[27]

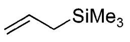
Results and Discussion

The Relative Nucleophilicities of Me$_3$SiCN and Allyltrimethylsilane. We were curious to see whether the inconsistent behavior observed between the reactions of allyltrimethylsilane and Me$_3$SiCN with acetal **1** was a general phenomenon. Experiments with the analogous five-membered ring acetal **3** (eq 2) confirmed that the trend was general. Consistent with the stereoelectronic model explaining nucleophilic additions to five-membered ring oxocarbenium ions,[28] treatment of **3** with allyltrimethylsilane in the presence of a Lewis acid afforded the allylated product with high 1,4-cis diastereoselectivity.[29] The reaction of acetal **3** with Me$_3$SiCN in the presence of a Lewis acid, however, proceeded with poor stereoselectivity.



(2)

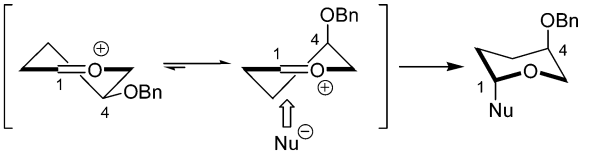
3 1,4-cis **4a** 1,4-trans **4b**

Nu−SiMe$_3$	**4a** : **4b**[a]	yield (%)[b]
	90 : 10	87
N≡C−SiMe$_3$	50 : 50	81

[a]Measured by GC analysis of unpurified reaction mixture. [b]Based on purified products.

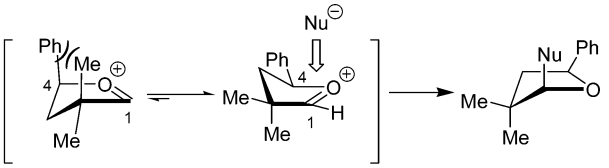
The allylation reactions of acetals **1** and **3** reflect the stereoelectronically controlled additions of the nucleophile to the low-energy conformations of the cyclic oxocarbenium ion intermediates. The intermediate derived from acetal **1** preferentially adopts the pseudoaxial conformation **5ax** (Scheme 1) due to the stabilizing electrostatic interactions between the partially negatively charged atom of the substituent and the positively charged carbon of the oxocarbenium ion.[30−32] Nucleophilic attack to **5ax** by a pathway proceeding through a chairlike transition-state structure affords the observed 1,4-trans product **2b**.[33−35] Similarly, the five-membered ring oxocarbenium ion derived from acetal **3** preferentially adopts the low-energy diequatorial conformation **6eq** over the sterically congested conformation **6ax** (Scheme 2). Nucleophilic addition to **6eq** by a pathway that proceeds through a staggered transition-state structure leads to the observed 1,4-cis substituted product **4a**, as described by Curtin-Hammett kinetics.[29,34,35]

Scheme 1. Nucleophilic Addition to Six-Membered Ring Oxocarbenium Ions



5eq **5ax** **2b**

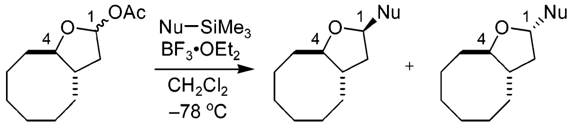
Scheme 2. Nucleophilic Addition to Five-Membered Ring Oxocarbenium Ions



6ax **6eq** **4a**

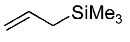
The discrepancy between the high diastereoselectivity observed for allylations and the low selectivity observed for cyanations (eqs 1 and 2) cannot be inferred from stereoelectronic models. The relative ground-state populations of the oxocarbenium ion conformers **5** and **6** should be independent of the type of nucleophile employed. Consequently, the loss of diastereoselectivity observed for reactions involving Me$_3$SiCN suggests a loss of facial preference for nucleophilic addition to these cations.

The reactions of bicyclic acetal **7** demonstrate that Me$_3$SiCN adds to oxocarbenium ions with no stereoelectronic preference. Because the oxocarbenium ion derived from this acetal is conformationally constrained, the facial selectivity reveals the inherent stereoelectronic preference of the nucleophile.[28] The substitution reactions of acetal **7** revealed a similar trend to that observed for acetals **1** and **3** (eqs 1 and 2): allylation proceeded with high diastereoselectivity, but formation of the nitrile product occurred with low selectivity (eq 3).[28]



(3)

7 1,4-cis **8a** 1,4-trans **8b**

Nu−SiMe$_3$	**8a** : **8b**[a]	yield (%)[b]
	93 : 7	83
N≡C−SiMe$_3$	54 : 46	92

[a]Measured by GC analysis of unpurified reaction mixture. [b]Based on purified products.

The loss of diastereoselectivity in the cyanation of the conformationally constrained acetal **7** confirmed that Me$_3$SiCN

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(23) Loos, R.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2003**, *125*, 14126−14132.

(24) Tishkov, A. A.; Mayr, H. *Angew. Chem., Int. Ed.* **2004**, *44*, 142−145.

(25) Tishkov, A. A.; Schmidhammer, U.; Roth, S.; Riedle, E.; Mayr, H. *Angew. Chem., Int. Ed.* **2005**, *44*, 4623−4626.

(26) The reactivity of ambident nucleophiles has traditionally been rationalized on the basis of the hard-soft acid-base principle: (a) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533−3539. (b) Pearson, R. G.; Songstad, J. *J. Am. Chem. Soc.* **1967**, *89*, 1827−1836.

(27) For examples of the loss of selectivity in the addition reactions of nucleophiles to highly reactive cationic intermediates at the rates of diffusion in aqueous media, see: (a) Young, P. R.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 8238−8248. (b) Kemp, D. S.; Casey, M. L. *J. Am. Chem. Soc.* **1973**, *95*, 6670−6680.

(28) Smith, D. M.; Tran, M. B.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 14149−14152.

(29) Smith, D. M.; Woerpel, K. A. *Org. Lett.* **2004**, *6*, 2063−2066.

(30) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859−864.

(31) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7587−7604.

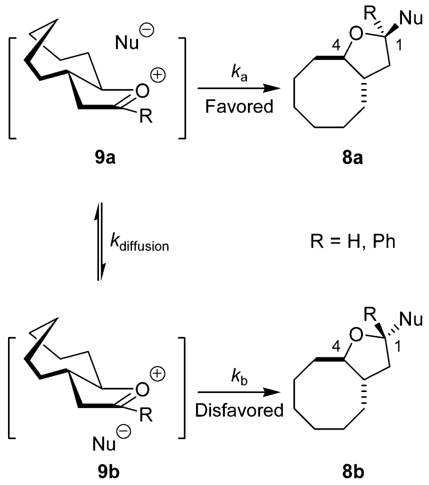
(32) Chamberland, S.; Ziller, J. W.; Woerpel, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 5322−5323.

(33) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169.

(34) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83−134.

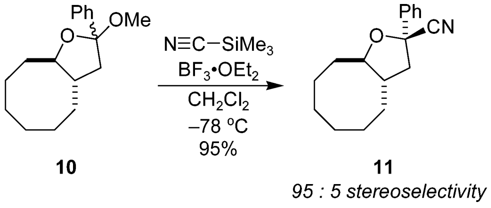
(35) Seeman, J. I. *J. Chem. Educ.* **1986**, *63*, 42−48.

Scheme 3. Nucleophilic Additions to Bicyclic Acetal **7**



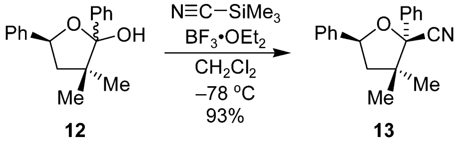
reacted without stereoelectronic preference for addition to one diastereotopic face of the cationic intermediate. One explanation that is consistent with these observations would be if the rate of nucleophilic addition to the top face (k_a) and the bottom face (k_b) of oxocarbenium ion **9** is faster than the rate of diffusion of the nucleophile between the two diastereotopic faces ($k_{diffusion}$, Scheme 3). In this case, the diastereoselectivity is determined by the relative rates of formation of the two nucleophile−electrophile complexes, **9a** and **9b**, and not the relative rates between the stereoelectronically favored and disfavored additions (k_a vs k_b). The extremely high electrophilicity of oxocarbenium ions renders such a scenario possible.[18,19,36,37]

The correlation between reactivity and stereoselectivity can explain the increase in diastereoselectivity observed in the nucleophilic addition reactions of Me_3SiCN with less reactive electrophiles. The reactions of Me_3SiCN with the C-1 phenyl-substituted bicyclic acetal **10** and the C-1 phenyl-substituted five-membered ring acetal **12** proceeded with high diastereoselectivity (eqs 4 and 5). A decrease in the ground-state energy of the oxocarbenium ion intermediate due to resonance stabilization from the C-1 phenyl substituent should decrease the rates of nucleophilic addition to the oxocarbenium ions **9a** and **9b** (k_a and k_b, Scheme 3) but not affect the rate of nucleophile diffusion between the two diastereotopic faces ($k_{diffusion}$, Scheme 3). Highly selective additions of Me_3SiCN to stabilized electrophiles such as *N*-acyliminium ions[38,39] and other benzylic oxocarbenium ions have also been observed.[40]



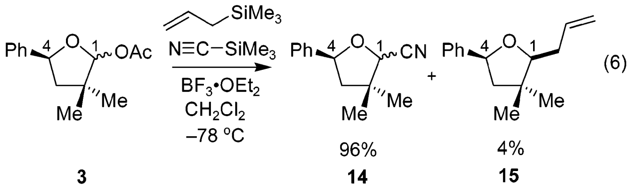
95 : 5 stereoselectivity

A competition experiment demonstrated that the disparity between the diastereoselectivities obtained from the additions



95 : 5 stereoselectivity

of allyltrimethylsilane and Me_3SiCN to oxocarbenium ions lacking the stabilizing phenyl substituents may result from the higher relative reactivity of Me_3SiCN.[41] When acetal **3** was treated with 4 equiv each of allyltrimethylsilane and Me_3SiCN in the presence of a Lewis acid, the nitrile product **14** was formed as the major product (eq 6).[41] This competition experiment is consistent with the hypothesis that Me_3SiCN reacts with acetal **3** at a faster rate than allyltrimethylsilane.[42]



54 : 45 stereoselectivity

92 : 8 stereoselectivity

The correlation between nucleophilicity and loss of stereoselectivity has been noticed in related systems. Whereas cyclic oxocarbenium ions react selectively with allyltrimethylsilane[29,33,43−46] and silyl enol ethers,[47−49] reactions with more reactive nucleophiles such as silyl ketene acetals[50,51] lead to products with low diastereoselectivity.[12−14] The predominance of the cyanide adduct **14** in the competition experiment between allyltrimethylsilane and Me_3SiCN with acetal **3** also follows this trend (eq 6).[17]

Other competition experiments between allyltrimethylsilane and Me_3SiCN, however, demonstrated that understanding the differences in reactivity between these two nucleophiles required further analysis. When the competition experiment was repeated with the bicyclic acetal **7** and the tetrahydropyran acetal **1**, the reactions were not selective for which nucleophile trapped the oxocarbenium ions (eqs 7 and 8).[41,42] Both of these electrophiles are considerably less hindered than the geminally substituted acetal **3**, so the differences in the results for the competition experiments might be the result of steric influences (vide infra).

The lack of consistency between the competition experiments suggested that different mechanisms govern the nucleophilic addition of allylsilanes and silyl cyanides to the cationic

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(36) Sinnott, M. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 2026−2032.

(37) Banait, N. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1991**, *113*, 7951−7958.

(38) Meza-Leon, R. L.; Crich, D.; Bernes, S.; Quintero, L. *J. Org. Chem.* **2004**, *69*, 3976−3978.

(39) Schuch, C. M.; Pilli, R. A. *Tetrahedron: Asymmetry* **2002**, *13*, 1973−1980.

(40) Nishiyama, Y.; Katoh, T.; Deguchi, K.; Morimoto, Y.; Itoh, K. *J. Org. Chem.* **1997**, *62*, 9339−9341.

(41) Product ratios were determined by analysis of the ^1H NMR spectrum of the unpurified reaction mixture. Product diastereoselectivities were determined by GC analysis of the unpurified reaction mixture.

(42) The diastereoselectivities of nucleophilic substitutions obtained from the competition experiments were identical to those obtained from the individual reactions.

(43) Kozikowski, A. P.; Sorgi, K. L.; Wang, B. C.; Xu, Z. *Tetrahedron Lett.* **1983**, *24*, 1563−1566.

(44) Hosomi, A.; Sakata, Y.; Sakurai, H. *Carbohydr. Res.* **1987**, *171*, 223−232.

(45) Bear, T. J.; Shaw, J. T.; Woerpel, K. A. *J. Org. Chem.* **2002**, *67*, 2056−2064.

(46) Ayala, L.; Lucero, C. G.; Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2003**, *125*, 15521−15528.

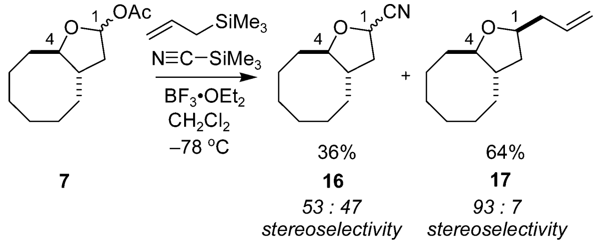
(47) Stewart, A. O.; Williams, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 4289−4296.

(48) Allevi, P.; Anastasia, M.; Ciuffreda, P.; Fiecchi, A.; Scala, A. *J. Chem. Soc., Chem. Commun.* **1987**, 1245−1246.

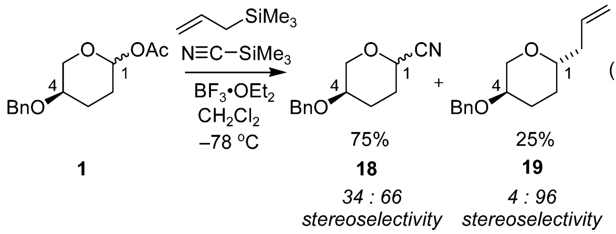
(49) Holmes, C. P.; Bartlett, P. A. *J. Org. Chem.* **1989**, *54*, 98−108.

(50) Tokuyasu, T.; Mayr, H. *Eur. J. Org. Chem.* **2004**, 2791−2796.

(51) Mayr, H.; Patz, M. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 938−957.



(7)

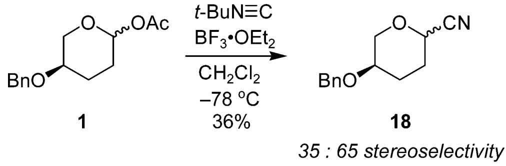


(8)

intermediates. The observation of allylated products **17** and **19** (eqs 7 and 8) was not consistent with the hypothesis that Me$_3$SiCN reacts with cyclic oxocarbenium ions faster than allyltrimethylsilane. Because the substitution reactions of allylsilanes with acetals **1**, **3**, and **7** are well understood,[28,29,46,52] the erratic results obtained from these competition experiments prompted our investigation into the mode of reactivity of silyl cyanides. Although Me$_3$SiCN is a common reagent utilized for cyanation,[17] the mechanism of its reactivity remains unclear.[53−55]

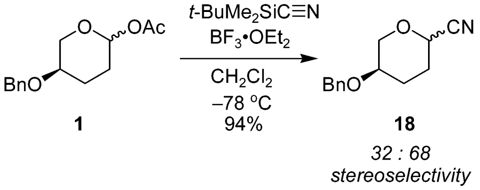
Understanding the Reactivity of Silyl Cyanides. Because the reactivity of Me$_3$SiCN appears to be highly substrate dependent,[29,38−40] specific details of our experimental approach to studying its reactivity deserve mention. We chose tetrahydropyran acetals bearing a single alkoxy substituent at the C-4 position as the electrophiles to study the reactivity of this nucleophile.[16] The reactions of these acetals are appealing because of the simplicity of their reactivity with nucleophiles.[30−32,52] Unlike the congested neopentyl center present in the oxocarbenium derived from acetal **3**, steric interactions between an approaching nucleophile and the C-4 ring substituent of the tetrahydropyran oxocarbenium ion should be minimal. The C-4 alkoxy substituent would also allow for mechanistic studies that provide unambiguous data about the involvement of reactive intermediates (vide infra).

Because trimethylsilyl isocyanide (Me$_3$SiNC) is present in solutions of Me$_3$SiCN,[56−59] we considered that the isocyanide was the reactive species. Silyl cyanides exist in an equilibrium between the N-bound and C-bound isomers, with the equilibrium lying highly in the favor of the C-bound form (∼0.05% Me$_3$SiNC is present in neat Me$_3$SiCN).[57,59] Because it was not possible to study the reactivity of silyl isocyanides directly, we turned our attention to their alkyl analogues. Treatment of acetal **1** with *tert*-butyl isocyanide (*t*-BuNC) in the presence of a Lewis acid provided the nitrile product **18** in low yield and with low diastereoselectivity (eq 9).[41,60] The ability of *t*-BuNC to serve as a nitrile donor supports the involvement of Me$_3$SiNC as the nucleophile in solutions of Me$_3$SiCN. Because so little silyl isonitrile is present in solution,[56,57,59] the reaction of Me$_3$SiCN through this species seemed unlikely, although its participation cannot be discounted.[56,59,61]

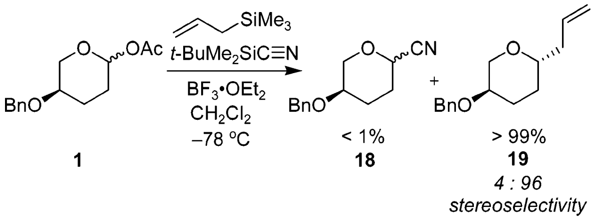


(9)

To investigate the role of nucleophilic activation of the silyl nucleophile, we turned our attention to the sterically congested cyanide donor *tert*-butyldimethylsilyl cyanide (*t*-BuMe$_2$SiCN). When acetal **1** was treated with *t*-BuMe$_2$SiCN in the presence of a Lewis acid, the nitrile product **18** was isolated as a 32:68 mixture of diastereomers (eq 10), consistent with the reaction of acetal **1** with Me$_3$SiCN (eq 1). Although *t*-BuMe$_2$SiCN is a competent nucleophile under these reaction conditions, when a competition experiment was conducted between allyltrimethylsilane and *t*-BuMe$_2$SiCN, only the allylated product **19** was isolated (eq 11).[41,42] This result contrasts with the competition experiment between allyltrimethylsilane and Me$_3$SiCN, in which both the allylated and cyanated products were observed (eq 8). The low reactivity of *t*-BuMe$_2$SiCN and acetal **1** in the presence of allyltrimethylsilane suggests that a reaction at the silicon atom may be required before the silyl cyanide can serve as a source of nucleophilic cyanide. The more congested *t*-BuMe$_2$SiCN would undergo such a reaction more slowly.[62]



(10)



(11)

The requirement for activation of silyl cyanides to generate a nucleophilic species also explains the results of the competition experiment between allyltrimethylsilane and Me$_3$SiCN with

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(52) Shenoy, S. R.; Woerpel, K. A. *Org. Lett.* **2005**, *7*, 1157−1160.

(53) Hertler, W. R.; Dixon, D. A.; Matthews, E. W.; Davidson, F.; Kitson, F. G. *J. Am. Chem. Soc.* **1987**, *109*, 6532−6533.

(54) Amurrio, I.; Córdoba, R.; Csákÿ, A. G.; Plumet, J. *Tetrahedron* **2004**, *60*, 10521−10524.

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(56) Me$_3$SiCN and Me$_3$SiNC interconvert rapidly on the ^{1}H NMR time scale in CH$_2$Cl$_2$ due to either solvent participation or impurities. The equilibrium between the two isomers strongly favors Me$_3$SiCN: Arnold, D. E. J.; Cradock, S.; Ebsworth, E. A. V.; Murdoch, J. D.; Rankin, D. W. H.; Skea, D. C. J.; Harris, R. K.; Kimber, B. J. *J. Chem. Soc., Dalton Trans.* **1981**, 1349−1351.

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(58) Georgiou, K.; Legon, A. C. *J. Mol. Struct.* **1982**, *78*, 257−263.

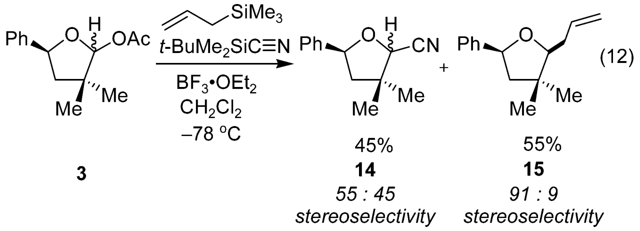
(59) Seckar, J. A.; Thayer, J. S. *Inorg. Chem.* **1976**, *15*, 501−504.

(60) Treatment of acetal **1** with trimethylacetonitrile did not afford the nitrile product **18**, suggesting that Me$_3$SiCN by itself is not the nucleophile.

(61) A competition experiment was performed by a reverse-addition of acetal **1** to a solution of allyltrimethylsilane and Me$_3$SiCN, with the rate of addition such that the concentration of Me$_3$SiNC (based on concentrations given in ref 59) and allyltrimethylsilane was maintained at 100 times the concentration of the acetal **1**. The product ratios obtained from this experiment were identical to those obtained from the competition experiment depicted in eq 8. This experiment is inconsistent with Me$_3$SiNC serving as the nucleophile.

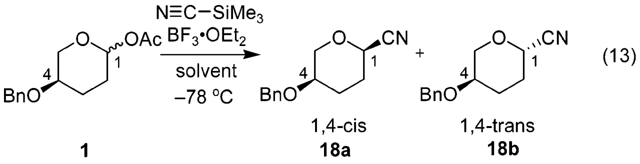
(62) *tert*-Butyldimethylsilyl ethers are considerably more stable towards nucleophilic attack than their trimethylsilyl analogues: Davies, J. S.; Higginbotham, C. L.; Tremeer, E. J.; Brown, C.; Treadgold, R. C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3043−3048.

acetal **3**, in which the nitrile product **14** was produced predominantly (eq 6). When the competition experiment was repeated using *t*-BuMe$_2$SiCN instead of Me$_3$SiCN, the reaction was not selective for which nucleophile trapped the oxocarbenium ion (eq 12).[41,42] The geminal substitution on the acetal **3** should decrease the reactivity of its resultant oxocarbenium ion **6** toward nucleophilic attack, allowing time for the activation of Me$_3$SiCN. When the sterically congested reagent *t*-BuMe$_2$SiCN was employed as the source of nucleophilic cyanide, this activation step becomes slow compared to the nucleophilic addition of allyltrimethylsilane to the oxocarbenium ion intermediate. Because this congested neopentyl center of acetal **3** is not present in the oxocarbenium ions derived from acetals **1** and **7**, nucleophilic addition of allyltrimethylsilane to the oxocarbenium ion intermediate occurs faster than activation of Me$_3$SiCN.



(12)

The effects of polar solvents on the selectivity of additions of Me$_3$SiCN to oxocarbenium ions indicate that activation provides an anionic nucleophile (eq 13). In polar solvents, anionic nucleophiles should be solvated and thus rendered less nucleophilic. This effect is analogous to the decreased nucleophilicity of anions in protic media.[63,64] The increase in diastereoselectivity with increase in solvent polarity observed in the nucleophilic substitution reaction of Me$_3$SiCN and acetal **1** (eq 13) is consistent with a solvent-mediated decrease in the reactivity of an anionic nucleophile. Because reactions between cations and anions will occur at much faster rates in nonpolar media,[21] the lower diastereoselectivities observed for the substitution reactions of Me$_3$SiCN in nonpolar solvents is consistent with the involvement of a highly reactive anionic nucleophile. The sensitivity of Me$_3$SiCN to solvent polarities indicates that decreasing reactivity increases selectivity, which is consistent with the hypothesis that these reactions proceed at or near the diffusion limit.[65] Neutral nucleophiles such as allyltrimethylsilane show no such dependence on solvent polarity.[28]



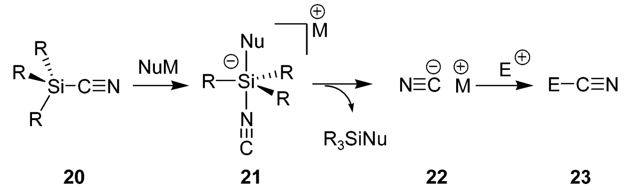
(13)

solvent	**18a : 18b**[a]	$E_T(30)$[b]	yield (%)[c]
PhMe	40 : 60	34.5	--
CH$_2$Cl$_2$	32 : 68	41.1	--
MeNO$_2$	14 : 86	46.3	--
CH$_3$CN	10 : 90	46.7	87

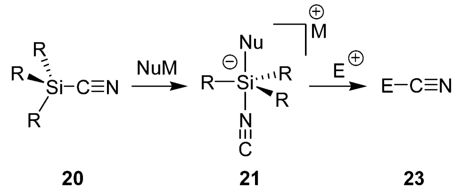
[a] Measured by GC analysis of unpurified reaction mixture. [b] $E_T(30)$ is a measure of empirical solvent polarity (ref 64). [c] Reported yields based on purified products.

Scheme 4. Mechanisms Involving the Activation of Silyl Cyanides

(a) Free Cyanide:



(b) Pentacoordinate Siliconate:



Two mechanisms integrating the requirements of activation of the silyl cyanides and the formation of a charged nucleophile are presented in Scheme 4. The first mechanism (a) involves nucleophilic attack on the silicon group of the silyl cyanide **20**, generating the pentacoordinate siliconate intermediate **21**. Subsequent elimination of the cyanide ligand would form free cyanide ion **22**. A second mechanism (b) involves the pentacoordinate siliconate intermediate **21** serving as the actual nucleophile.[66]

A three-phase test was used to probe the involvement of free cyanide (Scheme 4a). This experiment follows the work of Rebek and co-workers, who demonstrated the use of solid-supported reagents to detect free reaction intermediates.[67,68] The technique involves sequestering the nucleophilic and electrophilic reagents to different polymeric supports. Because functional groups bound to one solid support cannot interact with the functional groups bound to another solid support, any products arising from the reaction of two solid-supported reactants must involve free intermediates.[67,68]

The three-phase test provided definitive evidence indicating that free cyanide is not involved in the nucleophilicity of Me$_3$SiCN (Scheme 4a). Commercially available surface-modified polystyrene diethylsilane (PS-DES) was used to prepare the solid-supported cyanide **24** and solid-supported tetrahydropyran acetal **27** for use in the three-phase test.[69−71] Control experiments using each of these solid-supported reagents with their respective solution-phase counterparts demonstrated their competence under the reaction conditions used in the cyanation

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(63) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4th ed.; Kluwer Academic/Plenum: New York, 2000; pp 239−241.

(64) Reichardt, C. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 98−110.

(65) Mayr, H.; Ofial, A. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1844−1854.

(66) Another plausible mechanism for the reaction of Me$_3$SiCN with oxocarbenium ions involves the initial formation of an isonitrile, which can be converted to the nitrile through a subsequent isomerization. Although the interconversion between alkyl isocyanides and alkyl cyanides has been reported, this process requires high temperatures. See, for example: (a) Rüchardt, C.; Meier, M.; Haaf, K.; Pakusch, J.; Wolber, E. K. A.; Müller, B. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 893−901. (b) Boullanger, P.; Marmet, D.; Descotes, G. *Tetrahedron* **1979**, *35*, 163−167. (c) Schneider, F. W.; Rabinovitch, B. S. *J. Am. Chem. Soc.* **1963**, *85*, 2365−2370.

(67) Rebek, J., Jr. *Tetrahedron* **1979**, *35*, 723−731.

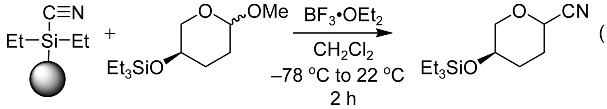
(68) Rebek, J., Jr.; Gavina, F. *J. Am. Chem. Soc.* **1975**, *97*, 3453−3456.

(69) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518−4521.

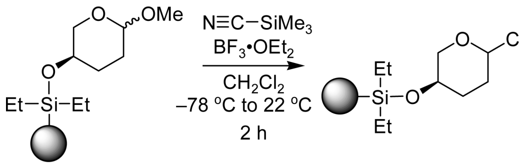
(70) Missio, A.; Marchioro, C.; Rossi, T.; Panunzio, M.; Selva, S.; Seneci, P. *Biotechnol. Bioeng.* **2000**, *71*, 38−43.

(71) Doi, T.; Sugiki, M.; Yamada, H.; Takahashi, T.; Porco, J. A., Jr. *Tetrahedron Lett.* **1999**, *40*, 2141−2144.

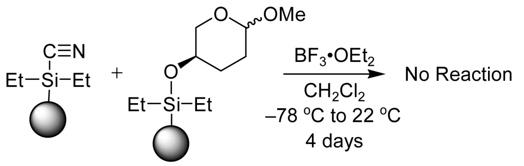
of cyclic oxocarbenium ions (eqs 14 and 15). When the two solid-supported reagents **24** and **27** were combined with each other in the presence of a Lewis acid, no cyanide transfer was observed, even after stirring the reaction mixture at room temperature for 4 days (eq 16). The three-phase test confirmed that the source of nucleophilic cyanide remains associated to the silicon, suggesting that upon activation, the silyl cyanide reacts through the pentacoordinate siliconate intermediate (Scheme 4b).



24 **25** **26** (14)

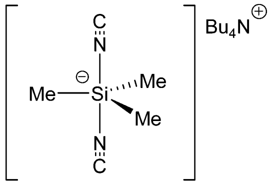


27 **28** (15)

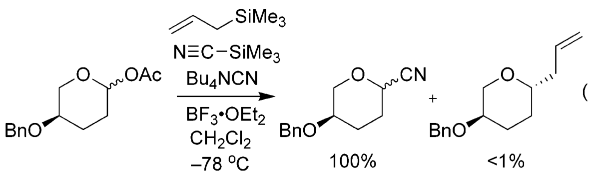


24 **27** (16)

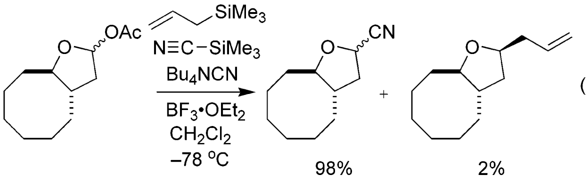
To study the nucleophilicity of siliconate intermediates, we focused our attention on biscyanosiliconate salts.[72] Treatment of Me_3SiCN with one molar equivalent of tetrabutylammonium cyanide (Bu_4NCN) is known to form tetrabutylammonium dicyanotrimethylsiliconate **29** as an isolable salt.[73] To examine the contribution of siliconate **29** to the nucleophilicity of Me_3SiCN, the tetrahydropyran acetal **1** and the bicyclic acetal **7** were treated with 4 equiv each of allyltrimethylsilane, Me_3SiCN, and Bu_4NCN (eqs 17 and 18). In both cases, the nitrile products **18** and **16** were produced as the major products of the reaction. Furthermore, the diastereoselectivity of the nitrile products formed in these reactions was comparable to the analogous competition experiments that lacked the Bu_4NCN additive (eqs 7 and 8).[41,42] The results of the previous competition experiments (eqs 6, 7, and 8) can be understood when considering that Me_3SiCN operates under a different mechanism than allyltrimethylsilane: Me_3SiCN must be activated to generate a nucleophilic species, whereas allyltrimethylsilane does not. When the activation of the silyl cyanide is faster than nucleophilic addition, competition experiments between allyltrimethylsilane and Me_3SiCN predominantly afford nitrile products.



29

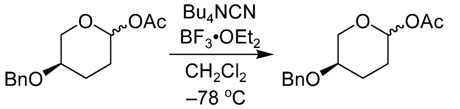


1 **18** **19** (17)

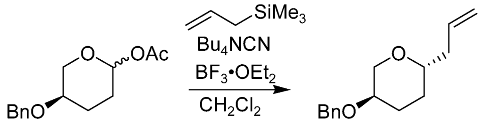


7 **16** **17** (18)

Control experiments determined that Bu_4NCN does not participate in these reactions as a source of nucleophilic cyanide. Treatment of acetal **1** with Bu_4NCN in the presence of a Lewis acid led to the recovery of starting material (eq 19). Furthermore, treatment of acetal **1** with allyltrimethylsilane in the presence of Bu_4NCN and Lewis acid did not affect the yield or diastereoselectivity of allylation (eq 20). When the three-phase test[67,68] was repeated with the addition of Bu_4NCN, no cyanide transfer was detected (eq 21). This negative three-phase test confirmed that the reactions of silyl cyanides do not involve free cyanide ion.

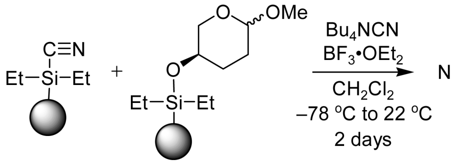


1 94% **reisolated** (19)



1 87% **19** (20)

96:4 stereoselectivity



24 **27** (21)

Taken together, the results of our investigation into the nucleophilic addition reactions of Me_3SiCN with cyclic oxocarbenium ions are consistent with the proposal that the bond-forming step of these reactions proceeds at or near the rate of diffusion. As reaction rates approach the diffusion limit, selectivity should deviate from the constant-selectivity relationship and become dependent upon reactivity.[21,51,65] Results with oxocarbenium ions stabilized by C-1 phenyl substituents (eqs 4 and 5) indicate that decreasing the reactivity of these electrophiles restores stereoelectronic control of their reactions with Me_3SiCN. The strong influence of solvent polarity on stereoselectivity, which is not the case with neutral nucleophiles, indicates a correlation between reactivity and selectivity. This correlation would be expected as reaction rates approach the diffusion limit.[51,65]

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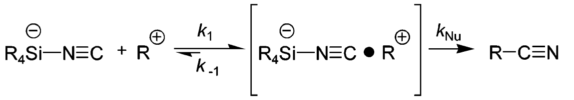
(72) Dixon, D. A.; Hertler, W. R.; Chase, D. B.; Farnham, W. B.; Davidson, F. *Inorg. Chem.* **1988**, *27*, 4012−4018.

(73) Sassaman, M. B.; Prakash, G. K. S.; Olah, G. A. *J. Org. Chem.* **1990**, *55*, 2016−2018.

The addition of Me$_3$SiCN to an oxocarbenium ion involves an anionic nucleophile and a cationic electrophile, which differs from the addition of neutral nucleophiles such as allyltrimethylsilane to the cationic intermediate. The reaction of ionic intermediates necessitates the consideration of initially formed ion pair **32** (eq 22), which should be more stable than the dissociated ions **30** and **31**.[74] There could be a barrier for the nucleophilic addition that forms nitrile **33**, but our data indicate that nucleophilic capture through ion pair **32** is fast relative to its dissociation ($k_{Nu} > k_{-1}$). Therefore, the selectivity for the formation of diastereomeric products **33** is dependent on the rate formation of the diastereomeric ion pairs **32** (k_1), not the rates of nucleophilic capture (k_{Nu}), consistent with our hypothesis (vide supra, Scheme 3).



$$\overset{\ominus}{R_4Si{-}N{\equiv}C} + R^{\oplus} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \left[\overset{\ominus}{R_4Si{-}N{\equiv}C}\bullet R^{\oplus}\right] \xrightarrow{k_{Nu}} R{-}C{\equiv}N \quad (22)$$

30 **31** **32** **33**

Conclusion

The failure of stereoelectronic models to account for the unusual behavior of silyl cyanides with highly reactive electrophiles such as oxocarbenium ions[18,19] is a result of the mechanism of these reactions, which differs from the mechanism of reactions of other common nucleophiles. The silyl cyanides require activation by a nucleophile in solution (such as the counterion of the Lewis acid or the leaving group of the acetal)[75] to form a pentacoordinate siliconate ion that transfers the cyano group. This activation step is slow relative to nucleophilic addition, as demonstrated through the competition experiments with the weakly nucleophilic allyltrimethylsilane. Once formed, however, the siliconate ion reacts with the electrophile at rates at or near the rate of diffusion. When reactions approach the diffusion rate limit, stereoelectronic effects cannot control the reaction outcome, because the stereochemistry-determining step occurs before bond formation. Stereoelectronic control over these reactions can be re-established by either stabilizing the charged intermediates (both the nucleophile and electrophile) in polar media or by structurally attenuating the electrophilicity of the oxocarbenium ion intermediate (eqs 4 and 5). These studies indicate that consideration of the reactivities of both the nucleophile and the electrophile is essential to using stereoelectronic models to predict reaction outcomes.

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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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(74) For example, perchlorate anion and the tetrabutylammonium cation are associated in CH$_2$Cl$_2$ ($K_A = k_1/k_{-1} = 3.4 \times 10^4$ M^{-1}): LeSuer, R. J.; Buttolph, C.; Geiger, W. E. *Anal. Chem.* **2004**, *76*, 6395−6401.

(75) Of the tetrabutylammonium salts examined (fluoride, chloride, bromide, iodide, acetate, and cyanide) Bu$_4$NCN gave the cleanest reactions.