Transition Structure Geometries for Transfers of Neutral and Anionic Nitrogen to Lithiated Carbanions

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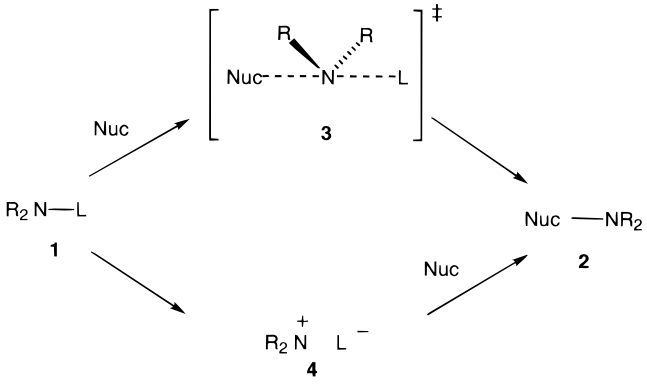
The geometries of nucleophilic substitutions at neutral and anionic nitrogen by organolithium species have been investigated. The demonstration of an intramolecular conversion of **9** to **10** provides an endocyclic restriction test which supports a trigonal bipyramidal transition structure for nitrogen transfer. A lack of isotopic scrambling of **12a**-^{18}**O** during nitrogen transfer is taken to rule out reaction via an oriented ion pair. Attempted endocyclic restriction tests for transfers of formally anionic nitrogen with **32** and **33** were not successful. Reactions of *n*-butyl, *s*-butyl and *tert*-butyllithium reagents with **16**, **23**, **30**, **31**, and **36**−**38** generally afford higher yields with increasing substitution at the carbon of the organolithium reagent and with decreasing substitution adjacent to the nitrogen of the aminating reagent. These results are consistent with trigonal bipyramidal transition states for nucleophilic displacements of oxygen by carbon at neutral and anionic nitrogen.

Introduction

Aminative processes which can be represented as nucleophilic displacements at nitrogen are reactions of mechanistic, synthetic, biochemical, and theoretical interest.[1−4] The limiting mechanisms for transfer of nitrogen from bonding to a leaving group to bonding to a first row nucleophile are illustrated by the conversion of **1** to **2**. In the concerted pathway bond making and bond breaking would occur simultaneously via **3**. This transition structure is shown as the trigonal bipyramid of a classic S_N2 substitution. An alternative pathway could involve initial bond cleavage to generate an intermediate, shown as the nitrenum ion,[4] which would react with a nucleophile in a second step. If the aminating reagent was an alkoxyamide anion, the concerted pathway would involve nucleophilic attack at a formally negative nitrogen while the stepwise process would proceed via a formal nitrenoid.



Kinetic evidence has been interpreted to favor concerted pathway for most aminations.[3] However kinetic data support a stepwise pathway for reactions in which an intermediate nitrenium ion can be stabilized by an aromatic ring.[5] The difference between the restricted geometry required by a trigonal bipyramidal transition structure, and the less constrained geometry of a dissociative pathway has been probed for aminations of lithiated carbanions by the endocyclic restriction test.[6] Those experiments revealed that displacements at both neutral and anionic nitrogen in small and medium-sized rings are intermolecular, consistent with the classic S_N2 pathway.[7] Theoretical calculations are also consistent with this interpretation.[2]

We now report investigations of transfers of nitrogen from oxygen to carbanions which could take place within large endocyclic rings. We also report studies of the effect of substitution on these nucleophilic displacements.

Results and Discussion

Reactions at Neutral Nitrogen. Endocyclic Restriction Test in a Large Ring. We have previously

(1) For reviews of electrophilic aminating reagents, see: Boche, G. *Houben-Weyl, Methods of Organic Chemistry, Vol. E21e*; Helmchen, G., Hoffmann, R. W., Mulzer, J., Eds.; Schauman, Thieme: Stuttgart, 1995; p 5133. Erdik, E.; Ay, M. *Chem. Rev.* **1989**, *89*, 1947. Mulzer, J.; Altenbach, H.-J.; Braun, M.; Krohn, K.; Reissig, H.-U. *Organic Synthesis Highlights*: VCH Publishers: Weinheim, 1991; p 45. Greck, C.; Genêt, J. P. *Syn. Lett.* **1977**, 741.

(2) McKee, J. *J. Am. Chem. Soc.* **1985**, *107*, 859. Armstrong, D. R.; Snaith, R.; Walker, G. T. *J. Chem. Soc., Chem. Commun.* **1985**, 789. Boche, G.; Wagner, H.-U. *J. Chem. Soc., Chem. Commun.* **1984**, 1591. Cramer, C. J.; Dulles, F. J.; Falvey, D. E. *J. Am. Chem. Soc.* **1994**, *116*, 9787. Bühl, M.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1993**, *115*, 9143. Bühl, M.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1993**, *115*, 364. Glukhovtseu, M. N.; Pross, A.; Radam, L.; *J. Am. Chem. Soc.*, **1995**, *117*, 9012.

(3) Helmick, J. S.; Martin, K. A.; Heinrich, J. L.; Novak, M. J. *Am. Chem. Soc.* **1991**, *113*, 3549. Ulbrich, R.; Famulok, M.; Bosold, F.; Boche, G. *Tetrahedron Lett.* **1990**, *31*, 1689. Campbell, J. J.; Glover, S. A. *J. Chem. Soc., Perkin Trans. 2* **1992**, 1661.

(4) For discussions of aminations related to carcinogenesis, see: Singer, B.; Kusmierek, J. T. *Annu. Rev. Biochem.* **1982**, *51*, 655. Lai, C. C.; Miller, E. C.; Miller, J. A.; Leim, A. *Carcinogenesis* **1987**, *8*, 471.

(5) Novak, M.; Kennedy, S. A. *J. Am. Chem. Soc.* **1995**, *117*, 574. Davidse, P. A.; Kahley, M. J.; McClelland, R. A.; Novak, M. *J. Am. Chem. Soc.* **1994**, *116*, 4513. Novak, M.; Kahley, M. J.; Lin, J.; Kennedy, S. A.; Swanegan, L. A. *Am. Chem. Soc.* **1994**, *116*, 11626. Defrancq, E.; Pelloux, N.; Leterne, A.; Lhomme, M.-F.; Lhomme, J. *J. Org. Chem.* **1991**, *56*, 4817. Robbins, R. J.; Laman, D. M.; Falvey, D. E. *J. Am. Chem. Soc.* **1996**, *118*, 8127.

(6) For a review of the endocyclic restriction test, see: Beak, P. *Acc. Chem. Res.* **1992**, *25*, 215.

(7) (a) Beak, P.; Basha, A.; Kokko, B. *J. Am. Chem. Soc.* **1984**, *106*, 1511. (b) Beak, P.; Basha, A.; Kokko, B. J.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016. (c) Beak, P.; Selling, G. W. *J. Org. Chem.* **1989**, *54*, 5574. (d) Beak, P.; Li, J. *J. Am. Chem. Soc.* **1991**, *113*, 2796.

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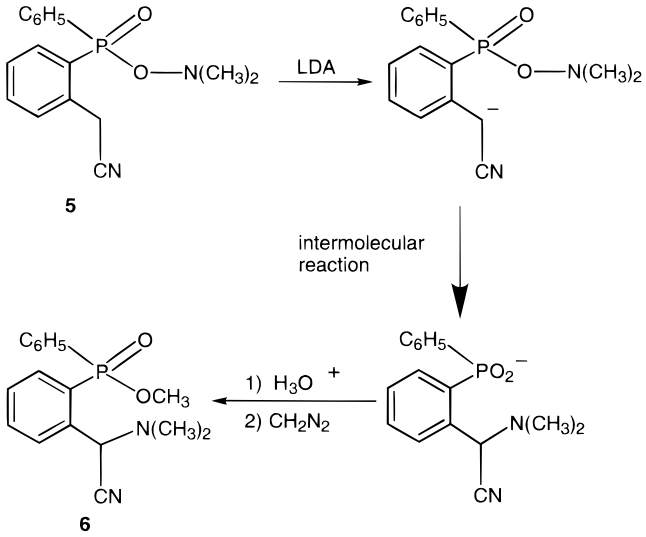
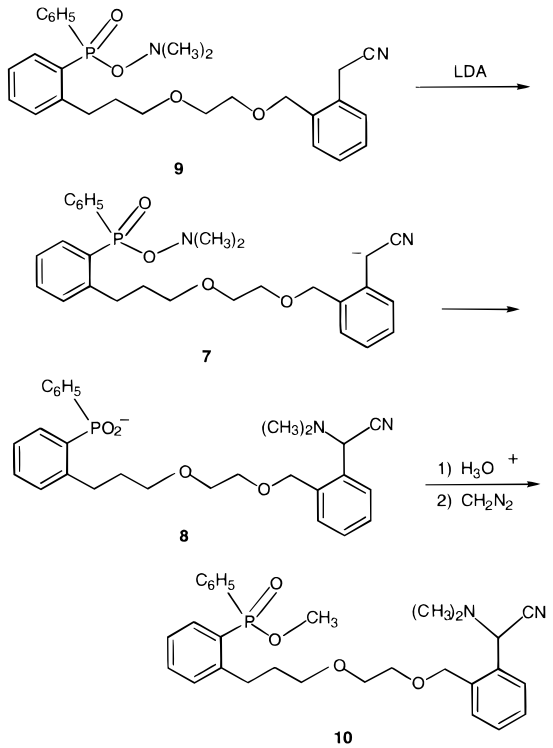
communicated our observation that the conversion of **5** to **6** is an intermolecular reaction based on double labeling of **5** and isotopic analysis which reveals isotopic scrambling in **6**.[7d,8] The inference from this endocyclic restriction test is that a large bond angle is required for nucleophilic displacement at nitrogen and the reaction proceeds via a trigonal bipyramidal transition structure.[9]



5 **6**

When a ring is of sufficient size to allow both the entering and leaving groups to be simultaneously apical in a trigonal bipyramidal transition structure, an intramolecular endocyclic reaction would be expected. We have carried out this study in a prospective 16-membered endocyclic ring for the conversion of **7** to **8** by investigation of the conversion of **9** to **10**.



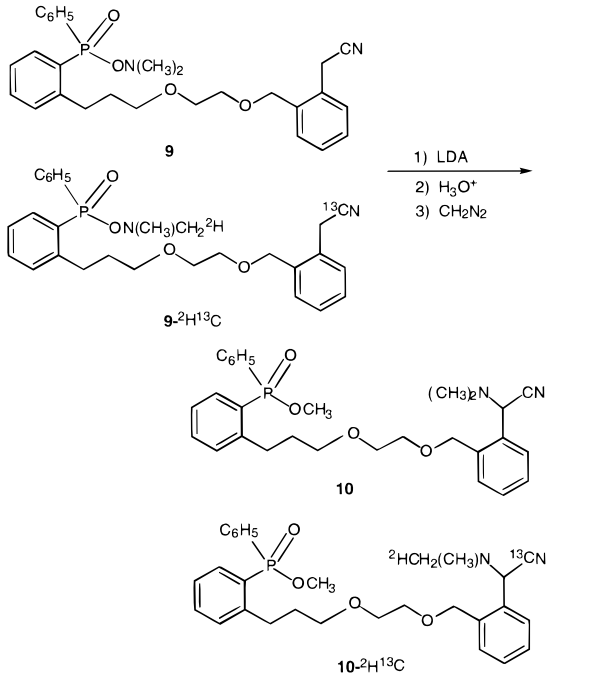
9 **7** **8** **10**

The synthesis of **9** was carried out in a eight-step sequence from readily available starting materials as shown in Scheme 1. The reactions in the scheme were straightforward except for the coupling reaction between the aryl iodide and dimethyl phenylphosphonite. Nickel chloride was not an effective catalyst, but with palladium acetate or palladium chloride as the catalyst, the reaction proceeded smoothly and provided the desired product in 82% yield.[10] The identity of **9** was established by spectroscopic data and elemental analysis. The doubly labeled compound **9**-^{2}H,^{13}C was prepared following the same procedure as for **9** using K^{13}CN (^{13}C = 99%) and HONCH$_3$-CH$_2$^{2}H (^{2}H = 97%) to incorporate the isotopic labels.

The authentic amination product **10** was also prepared from the reaction of **11** with **12** as shown in Scheme 2.

If we use effective molarity values of 0.01−0.05 for cyclization of a 16-membered ring, an intramolecular endocyclic reaction of **9** to give **10** should be accessible at ca. 0.001 M.[11] Using LDA, the benzylic carbanion **7** was generated from **9** at a concentration of 0.001 M. Workup of the reaction followed by reaction with diazomethane gave the substitution product **10** in 7% yield.

To determine the molecularity of the conversion of **9** to **10**, a double-labeling experiment was carried out with a ca. 1:1 mixture of unlabeled **9** and doubly labeled **9**-^{2}H^{13}C. The product **10** was obtained in ca. 10% yield. The isotopic distribution of the mixture of **10** and **10**-^{2}H^{13}C was determined by FABMS analysis and compared to the isotopic distribution of the reactant mixture of **9** and **9**-^{2}H^{13}C. The reactant isotopic composition was based on the weight of the unlabeled **9** and doubly labeled reactant **9**-^{2}H^{13}C.[12]



9 **9**-^{2}H^{13}C **10** **10**-^{2}H^{13}C

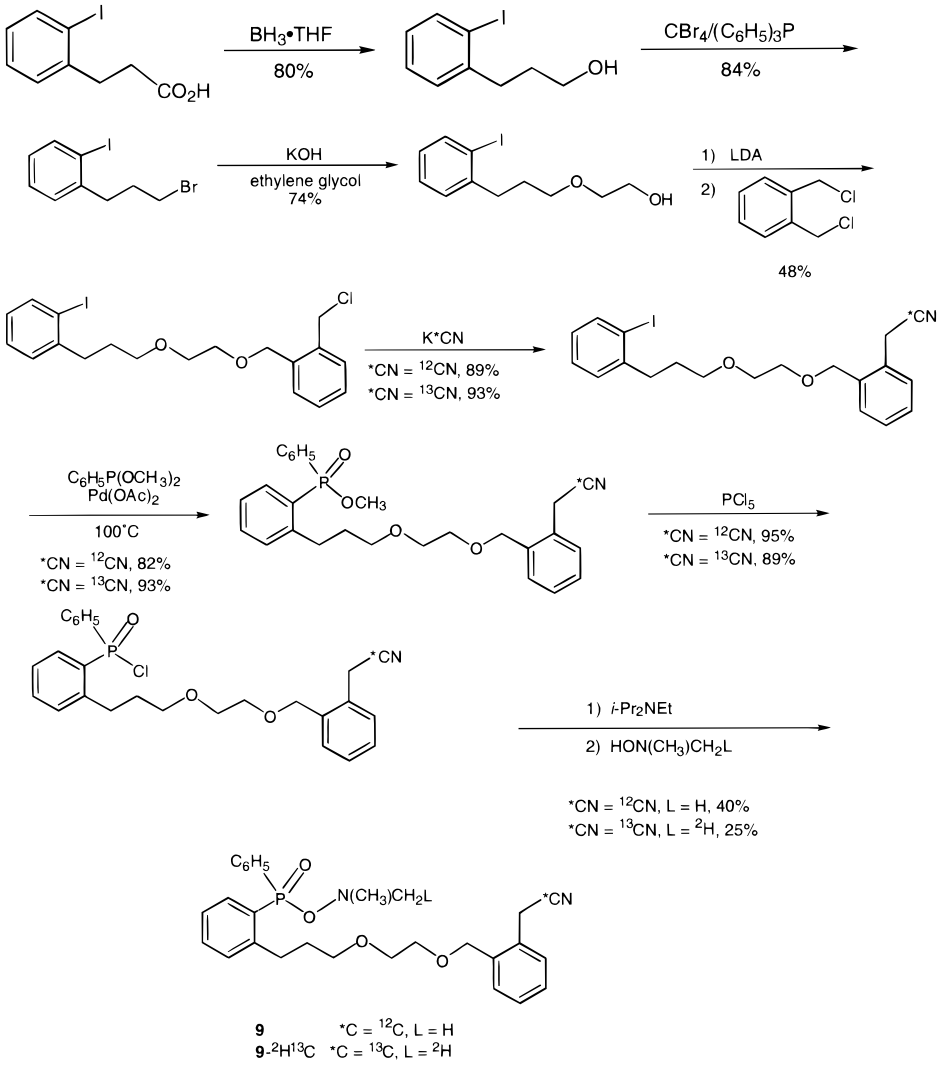
(8) For the use of the phosphinyl function to activate oxygen as a leaving group from nitrogen, see: (a) Boche, G.; Bernheim, M.; Schrott, W. *Tetrahedron Lett.* **1982**, 5399. (b) Colvin, E. W.; Kirby, G. W.; Wilson, A. C. *Tetrahedron Lett.* **1982**, 3835. (c) Ulbrich, R.; Famulok, M.; Bosold, F.; Boche, G. *Tetrahedron Lett.* **1990**, 1689.

(9) Discussion of these results and the experimental details are provided as supporting materials. See also: J. Li or K. Conser Ph.D. Thesis deposited with Michigan Microfilms Inc., Ann Arbor, MI.

(10) The use of nickel chloride as a catalyst to carry out this type of coupling reaction was first reported by Tavs and modified by Miles, Grabiak and Cummins, see: Tavs, P. *Chem. Ber.* **1970**, *103*, 2428. Miles, J. A.; Grabiak, R. C.; Cummins, C. *J. Org. Chem.* **1982**, *47*, 1677.

(11) Galli, C.; Illuminati, G.; Mandolini, L.; Tamborra, P. *J. Am. Chem. Soc.* **1977**, *99*, 2591. Illuminati, G.; Mandolini, L.; Masci, B. *J. Am. Chem. Soc.* **1977**, *99*, 6308. Casadei, M. A.; Galli, C.; Mandolini, L. *J. Am. Chem. Soc.* **1984**, *106*, 1051.

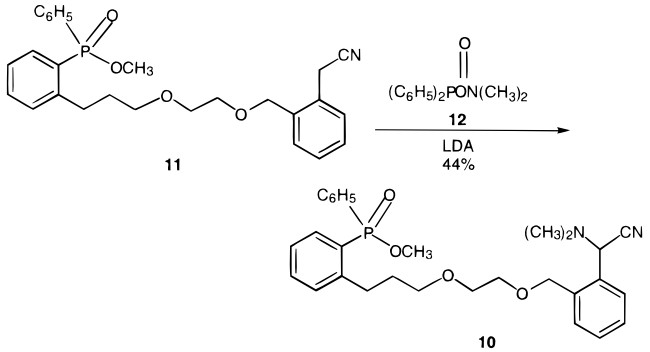
Scheme 1

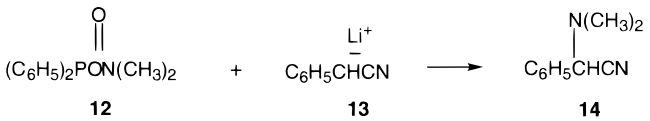


If the reaction proceeded by an intramolecular process, the product would be a mixture of **10** and **10**-$^{2}H^{13}C$ with the same isotopic distribution as that of the reactant mixture of **9** and **9**-$^{2}H^{13}C$. If the reaction proceeded by an intermolecular pathway, the products would be **10**, **10**-^{13}C, **10**-^{2}H, and **10**-$^{2}H^{13}C$ with a statistical distribution of the isotope. From the composition of the reactant mixture of **9** and **9**-$^{2}H^{13}C$, the isotopic compositions of **10** which would be expected for intramolecular and intermolecular processes are shown in Table 1, along with the experimentally determined values for two experiments. Comparison of the experimental values of the isotopic distribution to the calculated values show that the conversion of **7** to **8** occurs by an intramolecular pathway. The double-labeling experiments with **5** and **9** establish that there is a requirement for a large bond angle between the entering and leaving group in these nucleophilic substitutions at neutral nitrogen.

Test for an Ion Pair. The demonstration that there is a geometrical dependence for substitution at neutral nitrogen does not definitively rule out a reaction intermediate. An oriented ion pair, formed by a dissociation in which the leaving group shields the front side of the nitrogen from reaction with the nucleophile, could be envisioned. In an effort to detect an ion pair in the transfer of nitrogen from **12** to the anion of benzylcyanide **13** to give **14,** we have carried out an oxygen-18 labeling experiment.

Scheme 2





(12) We were unable to directly measure the isotopic ratio of the reactant mixture, because a molecular ion was not observed by FIMS (M^+) or FABMS ($M + H)^+$. Only the corresponding phosphinic acid was detected.

Table 1. Comparison of Isotopic Distribution of the Conversion of 9 to 10 for the Double-Labeling Experiments

	isotopic distribution (%)		
	$^2H^{13}C$	$^2H^{12}C$ and $^1H^{13}C$	$^1H^{12}C$
initial reactant[a] 9 + **9**-$^2H^{13}C$	40	2	57
product mixture **10** + **10**-$^2H^{13}C$			
intramolecular reaction[b]	40	2	57
intermolecular reaction[b]	17	48	34
experimental value[c]	42	3	56
initial reactant[a] **9** + **9**-$^2H^{13}C$	53	2	45
product mixture **10** + **10**-$^2H^{13}C$			
intramolecular reaction[b]	53	2	45
intermolecular reaction[b]	29	50	21
experimental value[c]	52	6	42

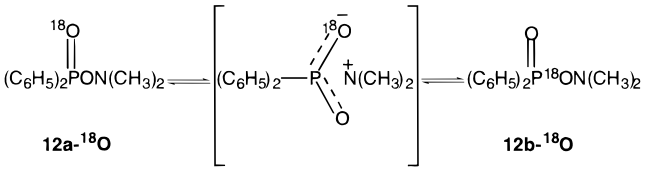
[a] Based on the weights of reactants in the mixture of 9 + 9-$^2H^{13}C$. [b] Based on the estimated isotopic distribution of the reactant mixture. [c] Determined by FABMS (±5%).

Table 2. Oxygen-18 Content in Reactant and Recovered 12-^{18}O[a]

from reactant **12a**-^{18}O	from recovered **12a**-^{18}O
47	49
47	46

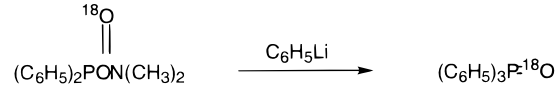
[a] Determined by FIMS (±5%).

Substitution reactions at the nitrogen of **12** have been shown to proceed with second-order kinetics by Boche and co-workers.[8c] If the reaction of **13** with **12** is also a second-order reaction and proceeds via a nitrenium ion pair, the rate-determining step must be nucleophilic attack by the carbanion nucleophile on the ion pair. In that case, the ion pair from the reactant **12a**-^{18}O would be expected to have a sufficient lifetime to undergo isotopic scrambling by recombination to afford **12b**-^{18}O with scrambling of the label.[13]



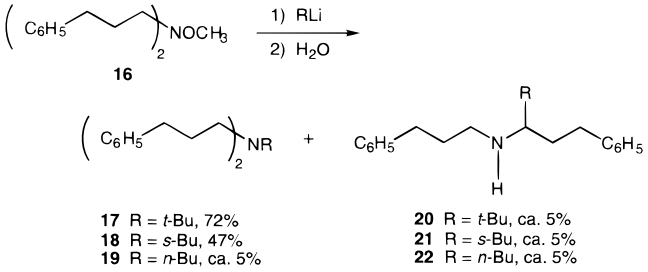
12a-^{18}O **12b**-^{18}O

Treatment of **12** with **13**, generated in situ from benzyl cyanide with LDA, gave the substitution product **14** in 65% yield.[14] Labeled material **12a**-^{18}O with 47% ^{18}O, as established by reaction of **12a**-^{18}O with phenyllithium and analysis of the label in the triphenyl phosphine oxide (**15**-^{18}O) produced, was prepared. Reaction of **12a**-^{18}O with **13** was carried out twice for different reaction times to give **14** in 28 and 39% yields, respectively, with recovery of **12**-^{18}O in 37 and 17% yields, respectively. The oxygen-18 content in the P═^{18}O position of the recovered **12a**-^{18}O, was determined by mass spectrometric analysis of **15**-^{18}O, obtained by reaction of the recovered **12**-^{18}O with phenyllithium. As shown in Table 2 this material was found to have 49 and 46% ^{18}O, consistent with that in the initial reactant. These data establishes that oxygen scrambling did not occur during the course of the substitution at nitrogen of **12a**-^{18}O. We take these results to rule out the dissociative nitrenium ion-pair pathway for nitrogen transfer in the reactions of **5** and **9**, as well as of **12**.



12a-^{18}O **15**-^{18}O

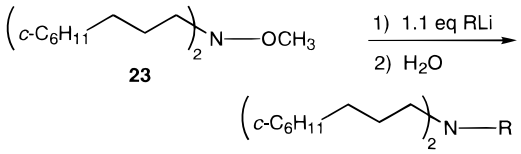
Reaction at Neutral Nitrogen. Effects of Steric Hindrance. We have found that the yields of substitution products in intermolecular displacements are dependent on the structure of the organolithium reagent and the *O*-alkyl dialkyl hydroxylamine.[15] The reaction of *N*,*N*-bis(3-phenylpropyl)-*O*-methylhydroxylamine (**16**) with *t*-BuLi, *s*-BuLi, and *n*-BuLi in hexanes gave the substitution products **17**, **18**, and **19** in 72, 47, and ca. 5% yields, respectively, along with low yields of the elimination−addition products **20**−**22**.[16] In these reactions, the more substituted the organolithium reagent the higher the yield of product. A similar order was also observed in a reaction of **16** with a 1:1 mixture of *t*-BuLi and *n*-BuLi; only the substitution product **17**, from the reaction of *t*-BuLi, was obtained.



17 R = *t*-Bu, 72%
18 R = *s*-Bu, 47%
19 R = *n*-Bu, ca. 5%

20 R = *t*-Bu, ca. 5%
21 R = *s*-Bu, ca. 5%
22 R = *n*-Bu, ca. 5%

Aminations of the butyllithium reagents by *N*,*N*-bis-(3-cyclohexyl-*n*-propyl)-*O*-methylhydroxylamine (**23**) were also investigated. The substitution products **24** and **25** obtained with *t*-BuLi and *s*-BuLi in 45 and 9% yields, respectively, were characterized by ^1H and ^{13}C NMR and GC/MS. No substitution product was obtained from the reaction of **23** with *n*-BuLi.



24 R = *t*-Bu 45%
25 R = *s*-Bu 9%

(13) This type of oxygen scrambling process has been shown to be a sensitive test for detection of the ion pair intermediates for carboxylates, sulfonates, and phosphinate esters. Goering, H. L.; Levy, J. F. *J. Am. Chem. Soc.* **1964**, *86*, 120. Goering, H. L.; Briody, R. G.; Sandrock, G. *J. Am. Chem. Soc.* **1970**, *92*, 7401. Dietze, P. E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240. Givens, R. S.; Matuszewski, B.; Athey, P. S.; Stoner, M. R. *J. Am. Chem. Soc.* **1990**, *112*, 6016.

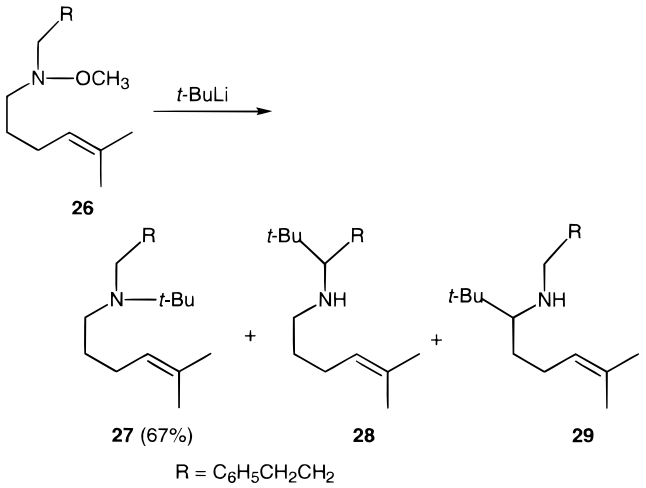
(14) Harger, M. J. P. *J. Chem. Soc., Chem. Commun.* **1979**, 768. Boche, G.; Sommerlade, R. H. *Tetrahedron* **1986**, 2703.

(15) For discussions of classic S_N2 substitutions at carbon, see: Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; Chapter 4. Streitwieser, A., Jr. *Solvolytic Displacement Reactions*; McGraw-Hill: New York, 1962; pp 2−92. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, 2nd ed.; Cornell University: Ithaca, NY, 1969; pp 421−610. Andreae, S.; Schmitz, E. *Synthesis* **1991**, 327. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 3rd ed.; Plenum Press: New York, 1997; pp 284−296.

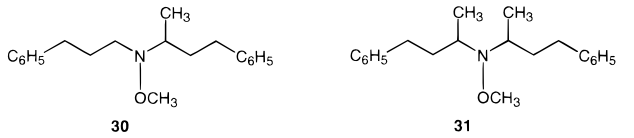
(16) The structural assignments to **19**−**22**, **28**, and **29** are provisional and based on GC-MS data, which gave the molecular ions as well as the characteristic α-cleavage at nitrogen. The latter five products are presumably formed by elimination of methoxide to give an imine, followed by addition of the organolithium reagent.[17]

The order of yields of substitution products could be taken to be indicate single electron transfer (SET) is a key step in the reaction. In a SET mechanism, transfer of an electron from the organolithium reagent could give a nitrogen radical anion, which could expel alkoxide to provide a nitrogen radical. This radical could couple with the residual alkyl radical formed from the organolithium.

We have attempted to detect the presence of a long-lived nitrogen radical by investigation of the reaction of **26**, a potential radical reporter system, with *t*-BuLi. This approach is based on the work of Newcomb et al. who established a rate of cyclization for an analogous radical as $10^5 s^{-1}$.[18] Reaction of **26** with *t*-BuLi gave a 67% yield of substitution product **27** and a ca. 5% mixture of **28** and **29**.[16] Since we did not detect any cyclized product from **26**, we did not obtain positive evidence for a long-lived radical intermediate. However the cyclization of this radical would be slow, and this result should not be taken as definitive evidence against a radical pathway.[18]

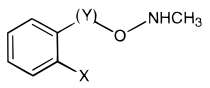


To determine the effect of substitutions on the *O*-alkylhydroxylamine, we have investigated the reactions of **30** and **31** with *t*-BuLi and *s*-BuLi. Substantial amounts of **30** and **31** were recovered from each attempted reaction with ony a trace of substitution product observed with *t*-BuLi. These results are taken to show that substituents a to nitrogen inhibit the substitution reactions of *N*,*N*-dialkyl-*O*-alkylhydroxylamines.



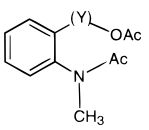
Reactions at Anionic Nitrogen. An Attempted Endocyclic Restriction Test in a Large Ring. Nucleophilic substitutions at formally anionic nitrogen have been known since the work of Sheverdina and Kocheshkov.[19] We have reported synthetic applications of such aminations for *N*-alkyl-*O*-alkylhydroxylamines in exocyclic intramolecular modes to provide four to seven membered rings.[7] We have also shown that for *N*-alkyl-*O*-alkyl hydroxylamines in which the reaction might proceed in an endocyclic five, six, or seven-membered ring, the nitrogen transfers are intermolecular.[20]

We have attempted to carry out endocyclic restriction tests for transfers of formally anionic nitrogen in rings of sufficient size to accommodate the entering and leaving groups in the apical positions of a trigonal bipyramid. Syntheses of **32** and **33**, as well as the acylated products of nitrogen transfer, **34** and **35**, respectively, were carried out.[9] Conversions of **32** and **33** to the corresponding dilithio intermediates were effected under a wide variety of conditions, and the reaction products were investigated. As detailed in the Supporting Information, the products which were identified showed cleavage of the ON bond, but we were unable to detect any **34** or **35** from these reactions.[20] Hence we have been unable to observe the intramolecular component of the endocyclic restriction test for substitutions at anionic nitrogen.



32 Y = $CH_2O(CH_2)_{12}$ X = I

33 Y = $(CH_2)_{12}$ X = Br

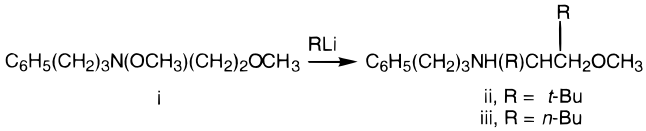


34 Y = $CH_2O(CH_2)_{12}$

35 Y = $(CH_2)_{12}$

Reaction at Anionic Nitrogen. Effects of Substitution. The effect of increasing substitution of the carbanion on the yields of amination products was evaluated by investigation of the reactions of **36**, **37** and **38** with *t*-BuLi, *s*-BuLi, and *n*-BuLi. Reactions carried out by initial treatment of **36** initially with MeLi at −78 °C, followed by addition of the BuLi and warming to −10 °C, gave the amine products, **39**, **40**, and **41** in 99, 60, and 68% yields, respectively. Aminations of *t*-BuLi and *s*-BuLi with **37** provided the amines **42** and **43** in 61 and 66% yields, respectively. Reaction of **37** with *n*-BuLi did not afford a substitution product. Reaction of the more substituted aminating reagent, *N*-(a-methyl)benzyl-*O*-methylhydroxylamine (**38**), with *t*-BuLi and *s*-BuLi gave the substitution products **44** and **45** in 30 and 35% yields in reactions which required warming. The elimination−addition products **46** and **47** were obtained in 7 and 25% yields, respectively. For reaction of *n*-BuLi with **38**, the elimination−addition product **48** was the only product observed.

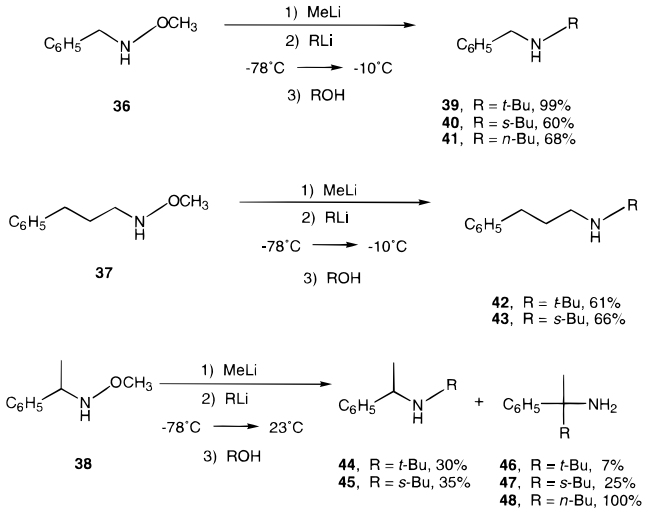
(17) (a) Kokko, B. J.; Beak, P. *Tetrahedron Lett.* **1983**, 561. (b) We have found that when *N*-(3-phenylpropyl)-*N*-(2′-methoxyethyl)-*O*-methylhydroxylamine (i) reacts with *t*-BuLi and *n*-BuLi, the elimination addition products ii and iii, are formed in yields of 77 and 82%, respectively. One interpretation is that a complex induced proximity effect is involved.[21]



(18) Newcomb, M.; Horner, J. H.; Shahin, H. *Tetrahedron Lett.* **1993**, *34*, 5523. Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *21*, 206, and references therein. Newcomb, M.; Glenn, A. G.; Manek, M. B. *J. Org. Chem.* **1989**, *54*, 4603. Newcomb, M.; Sanchez, R. M.; Kaplan, J. *J. Am. Chem. Soc.* **1987**, *109*, 1195. Walling, C.; Cooley, J. H.; Ponaras, A. A.; Racah, E. J. *J. Am. Chem. Soc.* **1966**, *88*, 5361. Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528. Newcomb, M.; Deeb, T. M. *J. Am. Chem. Soc.* **1987**, *109*, 3163. Newcomb, M.; Burchill, M. T. *J. Am. Chem. Soc.* **1983**, *105*, 7759.

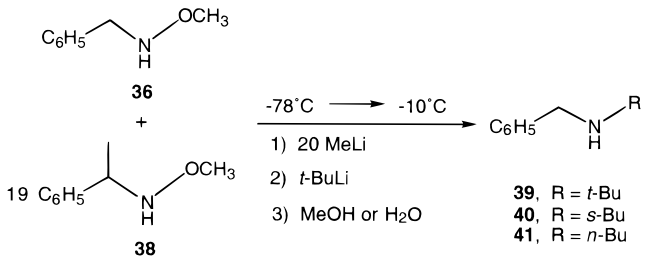
(19) Sheverdina, N. I.; Kocheshkov, Z. *J. Gen. Chem. USSR* **1938**, *8*, 1825.

(20) Self-decomposition of *N*-lithioalkoxides has been noted heretofore. (a) Beak, P.; Kokko, B. J. *J. Am. Chem. Soc.* **1982**, *45*, 2822. (b) Beak, P.; Kokko, B. J. *Tetrahedron Lett.* **1983**, *24*, 561.



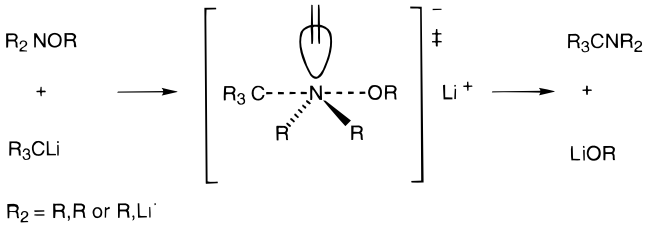
The trends in yields for reaction at the anionic nitrogen alkoxides do not show as much difference between the differently substituted carbanions as for reactions at neutral nitrogen (vide supra). To obtain a better measure of the competition between the butyllithiums, we carried out competitive reactions for **36**. A mixture of 1 equiv of MeLi and **36** was allowed to react with mixtures of excess of organolithium reagents. The product ratios were used to calculate the competitive efficiencies of the organolithium reagents toward amination by **36**, corrected for the change in the amount of each nucleophile available as a function of the extent of reaction.[9] We find that *t*-BuLi is ca. 9 times more effective in substitution than *n*-BuLi and slightly more effective than *s*-BuLi as a nucleophile for reactions with **36**.

The effect of steric hindrance adjacent to nitrogen on the yields of products has been investigated for competition between **36** and **38**. When a mixture of 19 equiv of **38** and 1 equiv of **36** was used for the amination of 1 equiv of *t*-BuLi, *s*-BuLi, and *n*-BuLi, the only products observed were **39**, **40**, and **41**, respectively, along with recovered **38**. In an experiment in which 4 equiv of **38** and 1 equiv of **36** were allowed to compete for the amination of 1 equiv of *n*-BuLi, analysis showed the presence of a small amount of **48** in addition to **41**. These results show the less sterically hindered **36** to be substantially more effective in amination than **38** for each of the butyllithium reagents.



These competitive efficiencies for substitution cannot be taken as rigorous measures of relative reactivity since we do not account to the rates of competing reactions. It is nonetheless interesting these results show that the yields of products are higher for the more substituted carbanions.

Scheme 3



Conclusions. Endocyclic restriction tests with **5** and **9** show that nucleophilic substitutions at neutral nitrogen requires a large angle between the nucleophile and the leaving group. A lack of isotopic scrambling in **12** excludes an oriented ion pair for these nucleophilic substitutions at neutral nitrogen. Although we were unable to carry out an endocyclic restriction test in a large ring for substitution at anionic nitrogen, the intermolecular reactions in the prospectively small endocyclic rings are consistent with a requirement for a large angle between the entering and leaving groups in these reactions also.[7] We suggest the transition states for substitution at neutral and lithiated nitrogen can be considered to be a trigonal bipyramidal structures resulting from nucleophilic attack from backside of the leaving group as shown in Scheme 3.[1,6,20] The competitive efficiencies in the neutral and anionic series, with increasing substitution at the carbonionic carbon of the nucleophiles affording increased yields of products, while increasing substitution adjacent to nitrogen of the electrophile leads to decreased yields, are consistent with trends bimolecular nucleophiles observed in substitutions at carbon.[22] The rationalizations of VSEPR and FMO theory which model the transition structures for classic S_N2 reactions are applicable and supported by more sophisticated theory.[2] For the reactions of the *N*-lithioalkoxy amides, the displacement at anionic nitrogen by a formal carbanion is considered to involve association with the lithium ions, a possibility which was recognized as an early case of the complex induced proximity effect.[1,6,20,21]

Acknowledgment. We are grateful to the National Science Foundation for support of this work.

Supporting Information Available: Details of the syntheses and reactions reported. This material is available free of charge via the Internet at http://pubs.acs.org.

JO990509G

(21) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356.

(22) Correlations of basicity and nucleophilicity have been observed in S_N2 reactions. For example, the nucleophilic constant of triethylamine is greater than that of ammonia. Increasing steric hindrance in the electrophile is well-known to decrease the rate of S_N2 substitutions at carbon.[15]