If 1 mol of H_2O_2 regenerates x mol of H_2O_2 which is incorporated additionally in the reaction cycle to produce x^2 mol of H_2O_2, total mol of H_2O_2 regenerated during the whole reaction should be expressed as

$$n_{re} = \sum_{s=1}^{\infty} x^s = x/(1 - x)$$

where $x = \alpha\beta\gamma$. The overall number of moles of H_2O_2 contributed to the whole reaction is

$$n(H_2O_2) = 1 + n_{re} = 1/(1 - x)$$

The regeneration of H_2O_2 will result in the apparent increase of oxygen uptake as well as the increasing consumption of benzene. At the same time, this will also cause the tracer content in phenol to have a smaller value than the gaseous content. The isotope content in phenol (η_p), when the regenerative cycle is taking place, should be

$$\eta_p = (y + 2xy + 2x\beta)/2(y + \beta)$$

where $y = \delta(1 - \beta)$. The parameter y stands for the fractional contribution of the diol path to the total phenol yield. It is obvious that if the diol path is ignored ($y = 0$), η_p becomes simply x.

In a similar manner, moles of benzene consumed (n_B) and the moles of phenol produced (n_p) are expressed in terms of above symbols as

$$n_B = \alpha/(1 - x)$$

$$n_p = \alpha(\beta + y)/(1 - x)$$

Since the last three variables, η_p, n_B, and n_p, were all determined experimentally to be 0.23 ± 0.05, 1.1 ± 0.02, and 0.5 ± 0.02, respectively, we tried to determine values of four unknown parameters of α to δ by computer simulation. Part of the result obtained is shown in Table III where the input data were fixed at $\eta_p = 0.23$, $n_B = 1.1$, and $n_p = 0.5$. Experimental values of η_p were, however, somewhat scattered and were 0.19 and 0.27 (see Table II). Even when a finite variation was allowed for the value of η_p, the acceptable range of each parameter was enlarged only slightly, as shown in column 2 of Table III.

Registry No. O_2, 7782-44-7; C_6H_6, 71-43-2; C_6H_5OH, 108-95-2; $FeSO_4$, 7720-78-7; H_2O_2, 7722-84-1; hydroxyl radical, 3352-57-6; benzoquinone, 106-51-4.

The Geometry of Displacements at Nonstereogenic Atoms: The Formal Displacement of Alkoxide from Alkoxyamines by Organolithium Reagents

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Received March 5, 1986

Abstract: Amination of organolithium reagents can be achieved by reaction with methyllithium–alkoxyamines. Details of the methodology and analysis of the reaction mechanism are presented. Reactions of methyl-, ethyl-, *n*-butyl-, *sec*-butyl-, *tert*-butyl-, phenyl-, and (*o*-methoxyphenyl)lithium with methyllithium–methoxyamine give the corresponding amines, isolated as the benzamides, in yields of 71–97%. Lower yields are obtained with *o*-lithio-*N*,*N*-diisopropylbenzamide, 4-lithiodibenzothiophene, *n*-butylmagnesium bromide, and phenylmagnesium bromide. Reactions of *n*-butyl-, *sec*-butyl-, *tert*-butyl-, and phenyllithium with methyllithium–*N*-methylmethoxyamine provide the corresponding *N*-methyl amines, isolated as the benzamides, in yields of 30–77%. Retention of the *N*-methyl group in these reactions is considered to rule out a nitrene intermediate. Involvement of a lithium alkoxyamide is suggested by the formation and substitution of that species by two different routes. Dilithiation of *N*-methoxy-*N*-[2-(*o*-bromophenyl)ethyl]amine (**17**) gives, after an intramolecular reaction and addition of acetyl chloride, *N*-acetylindoline, in 78% yield. Dilithiation of *N*-methyl-*N*-[2-(*o*-bromophenyl)ethoxy]amine (**19**) gives *N*-methyl-*N*-[*o*-(2-acetoxyethyl)phenyl]acetamide (**20**), after reaction with acetyl chloride. The nitrogen transfer in this conversion is shown by a double labeling experiment to be intermolecular. This result is taken to suggest that the bond angles required for displacement cannot be achieved in a six-membered ring, and the mechanism of the reaction involves a complex in which displacement occurs via an S_N2-like transition state. The exocyclic–endocyclic intramolecular–intermolecular test is noted to provide a general approach for deterimination of the geometry of reactions at nonstereogenic centers.

We have contributed to methodology for the amination of organolithium compounds by development of methyllithium–methoxyamine as a useful reagent.[1-3] The original reaction, discovered by Sheverdina and Kocheshkov for the conversion of one-half an equivalent of an organolithium or Grignard reagent with methoxyamine to the corresponding amine, has been used in a number of laboratories.[4,5] The overall process is a formal

Scheme I[a]

$$RLi \xrightarrow[(2)\ H_2O\ (3)\ C_6H_5COCl]{(1)\ 2CH_3Li\text{-}2CH_3ONH_2} RNHCOC_6H_5$$

[a] R = C_2H_5 (78%), *n*-C_4H_9 (71%, 77%[b]), *sec*-C_4H_9 (71%), *t*-C_4H_9 (80%[b]), $C_6H_5CH_2$ (97%), $CH_2{=}CHCH_2$ (78%), C_6H_5Li (90%), CH_3 (80%), *o*-$CH_3C_6H_4Li$ (96%), *o*-$CON(i\text{-}Pr)_2C_6H_4Li$ (14%[c]), 4-dibenzothiophenyl (55%[c]). [b] The solution was heated at reflux for 1 h. [c] The product is isolated as the amine.

(1) For summaries of the chemistry of aminations of nucleophiles including carbanions, see: Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, *1*, 1. Schmitz, E. *Russ. Chem. Rev.* **1976**, *45*, 16. Effenberger, F. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 151. Sheradsky, T. In *The Chemistry of Amino, Nitroso, and Nitro Compounds and Their Derivatives*; Patai, S., Ed.; Wiley: New York, 1982; p 395.
(2) Beak, P.; Kokko, B. J. *J. Org. Chem.* **1982**, *47*, 2822.
(3) Kokko, B. J.; Beak, P. *Tetrahedron Lett.* **1983**, *24*, 561.

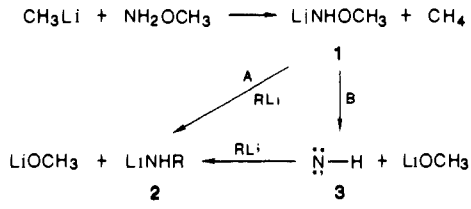
0002-7863/86/1508-6016$01.50/0

displacement of an alkoxy group, apparently from a lithium alkoxyamide, by the carbanionic nucleophile.

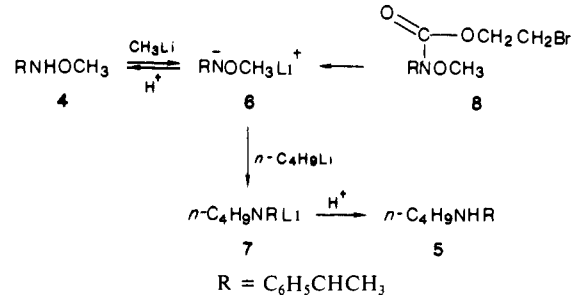
Formally similar aminations have been reported for Grignard reagents by reaction with chloramine,[6] for stabilized enolates with *O*-(2,4-dinitrophenyl)hydroxylamines,[7] and for lithium, Grignard, and copper reagents by *N,N*-dialkyl-*O*-sulfonylhydroxylamines[8] and *O*-(diphenylphosphinyl)hydroxylamines.[8d,9,10] Alternatively conversions of aromatic lithium and aromatic or aliphatic Grignard reagents to amines can also be accomplished by additions to the unsaturated nitrogen of azides,[11] diazo compounds,[12] or imine derivatives[13] followed by reduction of hydrolysis. In addition, an oxidative coupling of organocuprates, formed from organolithium reagents and secondary amines has been reported.[14]

The mechanism of displacement at formally saturated nitrogen by heteroatom nucleophiles is considered to be an S_N2 process.[1,6a,7c,15] In the case of methoxyamine, Erdik, in investigating the suggestion of Wakefield that 2 equiv of an organolithium could activate the amination reaction, proposed that reaction occurs between phenyllithium and dilithiated methoxyamine to give dilithioaniline.[16,17] The mechanism of the reaction of alkoxyamines with organolithium reagents does not appear to have been investigated otherwise.

Scheme II



Scheme III



In this report we provide details of the amination of organolithium reagents by lithium alkoxyamides.[2,3] We also establish that a lithium alkoxyamide is involved and rule out a nitrene mechanism. An exocyclic–endocyclic intramolecular–intermolecular test is shown to favor an S_N2-like reaction in an aggregated lithium complex.[18] This geometrical probe is noted to be generally applicable to investigation of reaction trajectories at nonsterogenic atoms.

Results and Discussion

Aminations with Methyllithium–Methoxyamine. Mechanistic consideration of the Sheverdina–Kocheskov amination, which seems to require 2 equiv of the organolithium reagent for 1 equiv of methoxyamine, suggests the first equivalent of the organometallic may act as a base.[4,5] We have found that methyllithium can serve as a surrogate first equivalent.[2] Thus a reagent produced by treatment of methoxyamine with methyllithium is effective for the conversions of primary, secondary, tertiary, alkyl, and aryl organolithium reagents to the corresponding amines as shown in Scheme I. The reaction is carried out by addition of the organolithium to be aminated to the reagent followed by warming to −15 °C for 2 h prior to the addition of water and workup. Most of the yields in the scheme are for isolation of the corresponding benzamide obtained by addition of benzoyl chloride after the quench. This procedure allows efficient characterization of the volatile amines without appreciable loss. In these experiments a twofold excess of the reagent is used because the reagent undergoes self-decomposition.[6,7c,15,19] The results in Scheme I show

(4) Sheverdina, N. J.; Kocheshkov, Z. *J. Gen. Chem. USSR* **1938**, *8*, 1825.
(5) Brown, R.; Jones, W. E. *J. Chem. Soc.* **1946**, 781. Willis, H. B. *Chem. Abstr.* **1944**, *38*, 739. Gilman, H.; Ingham, R. K. *J. Am. Chem. Soc.* **1953**, *75*, 4843. Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* **1946**, *68*, 1514. Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* **1946**, *68*, 580. Silver, M. S.; Shafer, P. R.; Nordlander, J. E.; Rüchardt, C.; Roberts, J. D. *J. Am. Chem. Soc.* **1960**, *82*, 2646. Silver, M. *J. Am. Chem.* T. **1961**, *83*, 3487. Yamada, S.-I.; Oquri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1972**, *10*, 623. Yamada, S.-I.; Oquri, T.; Shioiri, T. *Chem. Pharm. Bull.* **1975**, *23*, 167. Yamada, S.-I.; Oquri, T.; Shioiri, T. *J. Am. Chem. Soc.* **1975**, *23*, 173. For the similar use of *O*-benzylhydroxylamine, see: Sheverdina, N. I.; Kocheshkov, K. A. *Chem. Zentr.* **1942**, *1*, 1872. For *O*-2-tetrahydropyranylhydroxylamine, see: Yamada, S.-I.; Oquri, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1972**, *10*, 623. Yamada, S.-I.; Oquri, T.; Shioiri, T. *Chem. Pharm. Bull.* **1975**, *23*, 167. An example of a similar amination which is intramolecular and follows a β addition by methoxyamine is the conversion of α,β-unsaturated ketones to α keto aziridines with methoxyamine. Yamada, S.-I.; Shioiri, T.; Oquri, T. *Chem. Pharm. Bull.* **1975**, *23*, 173. Blatt, A. H. *J. Am. Chem. Soc.* **1939**, *61*, 3494. Cromwell, N. H.; Barker, N. G.; Wankel, R. A.; Vanderhorst, P. J.; Olson, F. W.; Anglin, J. H., Jr. *J. Am. Chem. Soc.* **1951**, *73*, 1044. Ponsold, K.; Drefahl, G.; Schönecker, B. *Chem. Ber.* **1964**, *97*, 2014.

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(10) Reactions of hydroxylamine-*O*-sulfonic acid and *O*-mesitylenesulfonylhydroxylamine with carbon nucleophiles are generally not effective although the former can be used to convert β-dicarbonyl system to pyrroles (Schmitz, E.; Jahnisch, K. *Z. Chem.* **1971**, *11*, 458. Tamura, Y.; Kato, S.; Ikeda, M. *Chem. Ind.* **1971**, 767). The latter is reported to aminate the soddium salt of methyldiethyl phosphonoacetate: Edwards, J. A.; Kluge, A. F.; Scopes, D. I. C. *J. Org. Chem.* **1977**, *42*, 376.

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methyllithium–methoxyamine is a synthetically useful aminating reagent for typical organolithium reagents.

If methyllithium is used in excess, methylamine can be obtained in 80% yield. Methylamine, from a few to 30%, is formed in the other reactions also. The low yield with *N,N*-diisopropyl-*o*-lithiobenzamide is attributed to steric hindrance, and an alternative approach is available for such cases.[11g] The yields are unaffected by the use of high or low halide methyllithium, by the addition of tetramethylethylenediamine, or by the use of hexane or tetrahydrofuran as the solvent for the lithium reagent. Reactions of *n*-butylmagnesium bromide and phenylmagnesium bromide under reflux for 1 h provide the corresponding amines in yields of 16 and 37%, respectively.

In an effort to determine the relative reactivities of organolithium reagents, mixtures of the different butyl- and phenyllithium reagents were allowed to react with a tenfold excess of methyllithium–methoxyamine. Thus 1:1 mixtures of *n*-C_4H_9Li/*sec*-C_4H_9Li, *sec*-C_4H_9Li/*t*-C_4H_9Li, and *sec*-C_4H_9Li/C_6H_5Li were found to provide product ratios of *n*-$C_4H_9NHCOC_6H_5$/*sec*-$C_4H_9NHCOC_6H_5$, *sec*-$C_4H_9NHCOC_6H_5$/*t*-$C_4H_9NHCOC_6H_5$, and *sec*-$C_4H_9NHCOC_6H_5$/$C_6H_5NHCOC_6H_5$ of 8:1, 1:90, and 1:90. However, reaction of a 1:1 mixture of *t*-C_4H_9Li and C_6H_5Li under the same conditions provides a 1:12 ratio of *t*-$C_4H_9NHCOC_6H_5$/$C_6H_5NHCOC_6H_5$ instead of the ca. 1:1 ratio expected on the basis of the earlier series. This intransitivity is precedented by work which shows that the relative reactivity of *tert*-butyllithium and iso-propyllithium in the lithiation of indene can depend on the composition of the aggregates even though kinetic regularity is maintained.[20] Such results provide a reminder of the need for caution in the interpretation of reactivities of organolithium species.

Reaction Mechanism. Two possible reaction mechanisms are shown in Scheme II. Initial deprotonation of methoxyamine by methyllithium is suggested to form the lithium alkoxyamide **1**. The next step, replacement of the alkoxide on nitrogen by the organolithium reagent to give the lithium amide **2**, can be discussed in terms of limiting mechanisms. A direct displacement, as shown for pathway A, is one end of the spectrum. Alternatively, a two-step sequence with a nitrene intermediate **3**, shown as pathway B, can be envisioned. Although pathway A is analogous to an S_N2 reaction at carbon, in this case it would involve displacement by a formal carbanion on a formal anionic center at the nitrogen. While pathway B is analogous to the reaction of nitrenes with nucleophiles, the proposed electron deficient intermediate **3**, nitrene itself, is not documented. In either case the amine product would result from protonation of the lithium amide **2**.

Deprotonation. The initial step postulated in Scheme II, formation of **1**, while reasonable, might not precede substitution. For example, a weak association complex in which the nitrogen is formally neutral and from which alkoxide could be displaced directly without negative charge repulsions is a possibility. Although the ^{13}C NMR spectrum of methane can be observed upon mixing methoxyamine and methyllithium, we were unable to show the reaction to be quantitative.[21]

Accordingly we have generated a lithium alkoxyamide by two different routes as shown in Scheme III. Reaction of *N*-methoxy-*N*-(1-phenylethyl)amine **4** with methyllithium followed by *n*-butyllithium gives *N*-*n*-butyl-*N*-(1-phenylethyl)amine **5** in 68% yield. Presumably the salt **6** is formed in the initial step and converted to lithium *N*-butyl-*N*-(1-phenylethyl)amide **7** in the second step. Alternatively treatment of the bromocarbamate **8** with 2 equiv of *tert*-butyllithium followed by addition of *n*-butyllithium gives **5** in 64% yield. In this case **7** is considered to be formed by halogen–metal exchange and loss of ethylene and carbon dioxide, although alternative routes to **6** are also possible. Confirmation of the formation of **6** from **8** was provided by a separate experiment in which addition of aqueous acid after treatment of **8** with *tert*-butyllithium provided the amine **4**. The intermediacy of **6** in the amination, rather than direct reaction of weak complexes, is most consistent with these results. However it must be noted this suggestion is circumstantial and awaits the definitive proof of direct observation.

Scheme IV

$$CH_3NHOCH_3 \xrightarrow{CH_3Li} CH_3\bar{N}OCH_3Li^+ \rightarrow CH_3\ddot{N}\cdot \quad \bar{O}CH_3Li^+ \rightarrow CH_2{=}NH$$

9 **10**

Scheme V[a]

$$RLi \xrightarrow[(2)\ H_2O\ (3)\ C_6H_5COCl]{(1)\ CH_3Li\text{-}CH_3NHOCH_3} RNCH_3COC_6H_5$$

[a] R = *n*-C_4H_9 (63%, 72%[b], 45%[c]), *sec*-C_4H_9 (62%), *t*-C_4H_9 (30%, 28%[d]), C_6H_5 (67%, 77%[b]). [b] 2 equiv of aminating agent were used. [c] Reaction without methyllithium. [d] The solution was heated at reflux for 2 h.

A Test of Pathway B. The Nitrene Intermediate. If the reaction of **1** proceeds via loss of alkoxide prior to carbon–nitrogen bond formation, a nitrene or nitrenoid intermediate would be involved, as suggested in pathway B. Diversion of such a species into alternative pathways might be expected and could provide a test of this mechanism.

Thus, for example, if the reaction of **6** involved a nitrene, 1,2-hydrogen migration or intramolecular addition to the aromatic ring might occur.[23] However, the products of such reactions were not observed. We have also found that reaction of 2 equiv of methyllithium–allyloxyamine with *n*-butyllithium gives, after treatment with benzoyl chloride, 95% *N,n*-butylbenzamide, 25% *N*-methylbenzamide, and 56% allyl benzoate. Again no diversion is apparent despite the fact the allyl double bond might be expected to add to a nitrene or nitrenoid.

$$NH_2OCH_2CH{=}CH_2 \xrightarrow{CH_3Li} LiNHOCH_2CH{=}CH_2 \xrightarrow{n\text{-}C_4H_9Li}$$

$$n\text{-}C_4H_9NHLi \xrightarrow{C_6H_5COCl} n\text{-}C_4H_9NHCOC_6H_5$$

In order to assess further the possibility of a nitrene intermediate, we have investigated aminations by *N*-methylmethoxyamine (**9**). Both theory and experiment suggest that 1,2-hydrogen migration in the methylnitrene singlet is spontaneous and without an activation barrier.[23,24] Thus, if as shown in Scheme IV, the loss of methoxide from the intermediate lithium alkoxyamide gives a singlet nitrene, hydrogen migration to give formimine (**10**) would be expected. Products from addition of the organolithium reagent to **10** or reduced yields of amination would result.[25]

The results of aminations of a series of organolithium reagents with 1 equiv of methyllithium–*N*-methylmethoxyamine are shown in Scheme V. The yields of the *N*-methyl-*N*-substituted amines with **9** are, except for the case of *tert*-butyllithium, comparable to those with **1**. No major diversions from direct amination have

(19) Presumably this is due to formation of diimine by self reaction of the methoxyamine–methyllithium and decomposition of that reactive species. Johnson, C. R.; Kirchhoff, R. A.; Corkins, H. G. *J. Org. Chem.* **1974**, *39*, 2458. Hunig, S.; Muller, H. R.; Thier, W. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 271. Karpitschka, E. M.; Knoflach, J.; Klötzer, W.; Baldinger, H. *Synthesis* **1982**, 592.

(20) Peascoe, W.; Applequist, D. E. *J. Org. Chem.* **1973**, *38*, 1510.

(21) We are grateful to Dr. S. G. Mills for carrying out this experiment.

(22) The fact that *N,N*-dimethyl-*O*-methoxyamine (i) undergoes elimination to give ii on treatment with methyllithium suggests **8** would undergo a similar fate if it were not converted fairly rapidly to 6.

$(CH_3)_2NOCH_3$ $CH_2{=}NCH_3$

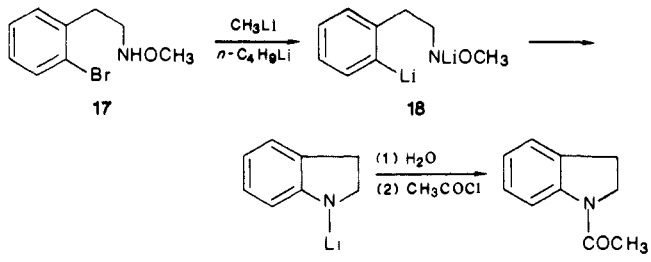
i ii

(23) *Azides and Nitrenes*; Scriven, E. F. V., Ed.; Academic Press: New York, 1984.

(24) Schaefer, H. F., III. *Acc. Chem. Res.* **1979**, *12*, 288. Demuynck, J.; Fox, D. J.; Yamaguchi, Y.; Schaefer, H. F., III *J. Am. Chem. Soc.* **1980**, *102*, 6204. Milligan, D. E. *J. Chem. Phys.* **1961**, *35*, 1491. Bock, H.; Dammel, R.; Horner, L. *Chem. Ber.* **1981**, *114*, 220. Pritzkow, V. W.; Timm, D. *J. Prakt Chem.* **1966**, *32*, 178. Lewis, F. D.; Saunders, W. H. In *Nitrenes*; Lwowski, W., Ed.; Interscience: New York, 1970; pp 47–97.

(25) Alternative processes involving methylnitrene which could give other products are conceivable. For example, intersystem crossing to triplet methylnitrene would be expected to give methylamine after hydrogen atom abstraction by the nitrene.

Scheme VI

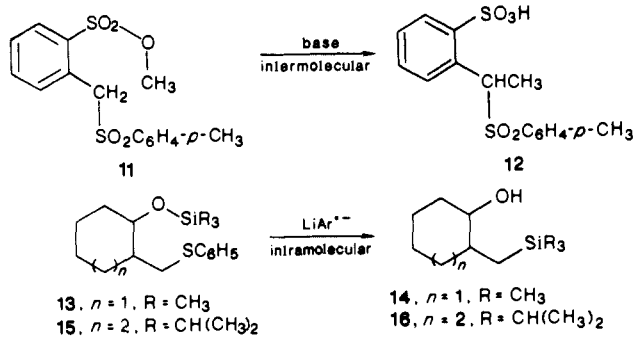


occurred and a divertable electron deficient nitrenoid species does not appear to be involved in the reaction. As heretofore the amines were isolated as the benzamides.

Synthetically these results provide the only methodology of which we are aware for direct conversion of an organolithium reagent to a secondary amine. The low yield with *tert*-butyllithium suggests that reaction may be difficult with sterically hindered systems. It is notable that 1 equiv of the aminating agent is almost as effective as an excess, suggesting that use of this methodology is efficient for either component.

A Test of Pathway A. The Geometry of Displacement at Nonstereogenic Atoms. If the displacement of the alkoxy group from the nitrogen of a lithium alkoxy amide by the carbon of an organolithium reagent is concerted, the most straightforward analogy, albeit one which ignores prospective charge repulsions, is to S_N2 displacement at carbon. In that case, reaction should proceed via a transition state in which the entering and leaving groups are ca. 180° to one another, and displacement occurs with inversion at the central atom. Indeed, of the tests used to distinguish limiting S_N1 and S_N2 reactions at carbon, that of geometry seems the most definitive.[26,27] In the case of nitrogen, the atom at which formal displacement takes place in functionally nonstereogenic so the transition-state geometry cannot be evaluated by analysis of reactant and product stereogenicity. However, the approach clearly delineated by Eschenmoser et al. for investigation of the geometry of displacement at carbon is applicable.[26]

The Swiss workers showed that the base-promoted conversion of **11** to **12** proceeded in an intermolecular mode because the ca. 180° bond angles required for S_N2 substitution at carbon cannot be achieved in the six-membered ring which would be required in the transition state of an intramolecular reaction. Illustrative contrasts are the reductive intramolecular conversions of **13** to **14** and **15** to **16**, reactions in which five-membered species are



credible as front side displacement at silicon is known to be possible.[28] We have extended this approach to determination of the geometry of the displacement by an organolithium reagent at the nitrogen of a lithium alkoxyamide by investigation of cases in which exo- and endocyclic transition states are conceivable.

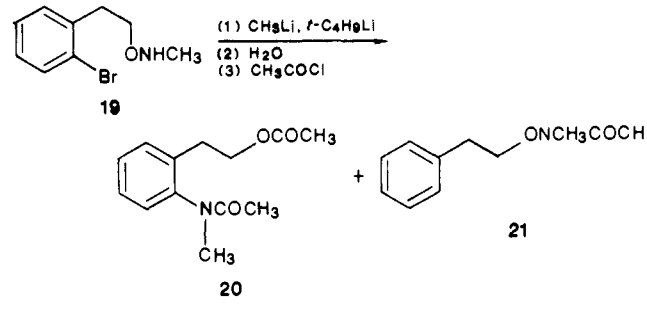
Reaction of *N*-methoxy-N-[2-(*o*-bromophenyl)ethyl]amine (**17**) with methyllithium and *n*-butyllithium at −78 °C followed by warming to −15 °C for 3 h, aqueous workup, and addition of acetyl chloride provides *N*-acetylindoline. Our purification was not efficient, for a 78% yield of crude material resulted in a 43% yield of analytically pure product. The reaction sequence is shown in Scheme VI. The first steps are considered to involve deprotonation and halogen metal exchange to provide **18** which undergoes an intramolecular displacement to give lithioindoline. The mechanism could proceed via either pathway A in a 5-exo-tet mode[29] or pathway B involving a nondivertable nitrenoid which is trapped intramolecularly.

Table I. Labeling for the Conversion of *N*-Methyl-*N*-[2-(*o*-bromophenyl)ethoxy]amine (**19**) to *N*-Methyl-*N*-[*o*-(2-acetoxyethyl)phenyl]acetamide (**20**)

reactant (%)[a] **19**				product (%)[a] **20**			
19	**19-d_2**	**19-d_3**		**20**	**20-d_1**	**20-d_2**	**20-d_3**
49	11	41	exptl	32	18	33	17
			inter[b]	29	20	30	21
			intra[c]	49		11	41
78	5	17	exptl	68	10	18	4
			inter[b]	65	13	18	4
			intra[c]	78		5	17

[a] The error is ±4%. [b] Calculated values based on **19**, **19-d_2**, and **19-d_3** for intermolecular reaction. [c] Calculated values based on **19**, **19-d_2**, and **19-d_3** for intramolecular reaction.

Determination of the effect of the geometry of the nitrogen oxygen bond on the reaction was carried out by investigation of *N*-methyl-N-[2-(*o*-bromophenyl)ethoxy]amine **19**. This compound on reaction with methyllithium and *tert*-butyllithium at −78 °C followed by warming to −15 °C for 3 h, aqueous workup, and reaction with acetyl chloride provides 7% of *N*-methyl-*N*-[*o*-(2-acetoxyethyl)phenyl]acetamide (**20**) and 11% of *N*-methyl-*N*-(2-phenylethoxy)acetamide (**21**).

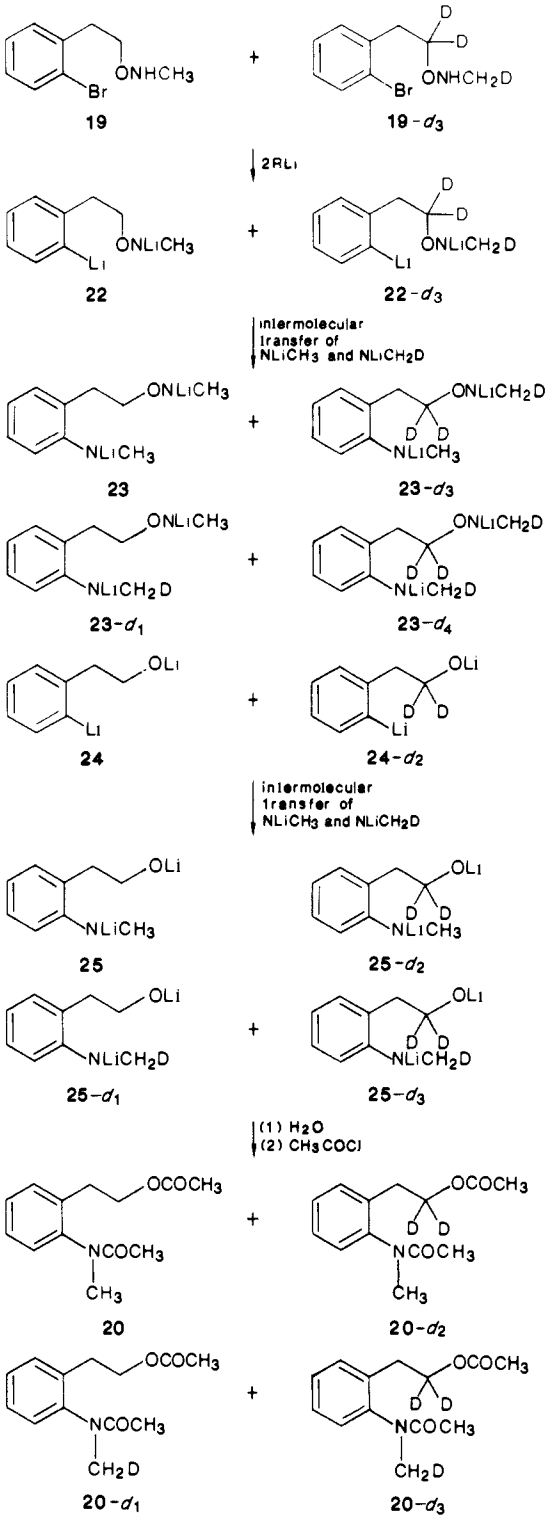


Although **20** could arise via either the displacement or nitrenoid pathways, these possibilities can be distinguished by a double labeling experiment with **19** and **19-d_3** as outlined in Schemes VIIand VIII. If the reaction occurs via pathway A and involves a formal nucleophilic displacement which requires a disposition of ca. 180° between the entering and leaving groups, an intermolecular pathway would be followed, and the crossover products in Scheme VII would be obtained. The initial lithiation reaction would provide **22** and **22-d_3**. Since the bond angles of the transition state requisite for displacement cannot be achieved intramolecularly in a six-membered ring, intermolecular reaction would be expected and give **23**, **23-d_1**, **23-d_3**, **23-d_4**, **24**, and **24-d_2**. A second round of intermolecular reaction between these species or other cleavage of the oxygen nitrogen bonds of **23** would provide **25**, **25-d_1**, **25-d_2**, and **25-d_3**. Evidence for this pathway would be isolation of a mixture of **20**, **20-d_1**, **20-d_2**, and **20-d_3**. Statistical distribution of the label would be expected, i.e., for a 1:1 mixture of **19**/**19-d_3** a 1:1:1:1 mixture of **20**/**20-d_1**/**20-d_2**/**20-d_3** would result.

The results expected for pathway B are shown in Scheme VIII. Since the nitrenoid intermediate would be short lived (vide supra), an intramolecular reaction would be expected. In this case **19** and **19-d_3** reacting via **26** and **26-d_3** would provide only **25** and **25-d_3** as precursors to **20** and **20-d_3**. The latter would be obtained in the same ratio as **19** and **19-d_3**; i.e., by this pathway **20-d_1** and

(26) Tenud, L.; Faroq, S.; Seibl, J.; Eschenmoser, A. *Helv. Chim. Acta.* **1970**, *53*, 2059.
(27) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*; Harper & Row: New York, 1981; Chapter 4.
(28) Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4349. Corey, E. J.; Rücker, C. *Tetrahedron Lett.* **1984**, *25*, 4345.
(29) For generalizations, see: Baldwin, J. E. Lusch, M. J. *Tetrahedron* **1982**, *19*, 2939 and references cited therein.

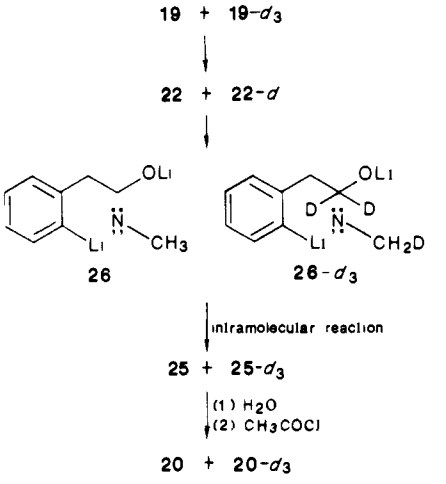
Scheme VII



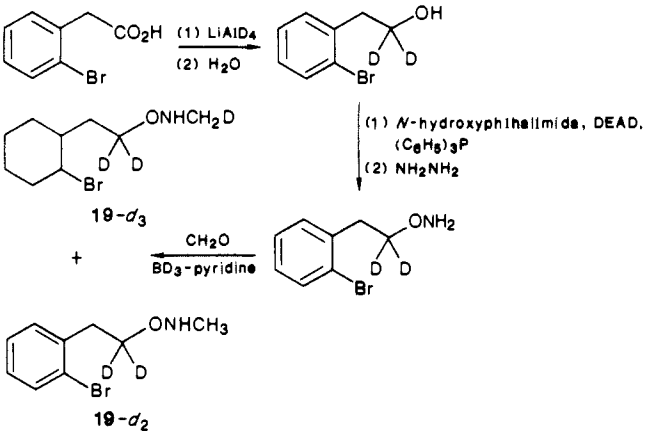
20-d_2 products would not be observed.

A mixture of labeled **19-d_3** and **19-d_2** was synthesized as shown in Scheme IX. The presence of **19-d_2** is attributed to incomplete labeling in the reduction step. Double labeling experiments were carried out as summarized in Table I by using two different mixtures of **19**, **19-d_2**, and **19-d_3**. Both **20** and **21** were isolated, and the isotopic distribution in these compounds was determined by mass spectroscopy. In the case of intermolecular reaction the ratio of **20**/**20-d_1**/**20-d_2**/**20-d_3** would be 29:20:30:21 in the first experiment and 65:13:18:4 in the second. In the case of intramolecular reaction, the isotopic composition of **20** would be the same as that of **19**. The results in the table show that product **20** has essentially statistical scrambling of the label.

Scheme VIII



Scheme IX



The product **21** has the same labeling as the reactant. In the first case this is 48:12:41 (±4%) and in the second it is 76:6:17 (±4%) for **21**, **21-d_2**, and **21-d_3**. The distribution of the label in **21** is significant because **21** arises from **22** which could conceivably equilibrate with **24** to provide scrambling of the label prior to nitrogen transfer.

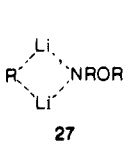
Our efforts to extend this study to Grignard reagents by treatment of **22** with magnesium bromide were unsuccessful. Transfer of nitrogen was not observed under a variety of conditions.

Our interpretation of the statistical distribution of the label in **20** is that the displacement is an intermolecular reaction. We suggest that these results indicate that the nucleophile preferentially approaches the nitrogen atom undergoing displacement at an angle such that the entering carbon and the leaving alkoxy group are disposed at ca. 180 °C to one another. The 6-endo-tet transition state which would be required for intramolecular reaction of **19** is then sufficiently strained that the reaction does not follow that route but occurs by an intermolecular reaction in which the requisite bond angles can be achieved. A 5-exo-tet process with ca. 180° bond angles is possible intramolecularly for **17**, and the reaction proceeds well. Such an alignment is consistent with a frontier orbital interaction between the HOMO of a nucleophilic carbon and the σ^* LUMO of the nitrogen oxygen bond. These results do not provide information about whether the bond formation is a one- or two-electron process within a reaction complex.[30] An $S_{RN}1$ reaction would require a radical anion intermediate with an electron in a σ^* orbital of a first row atom.[31]

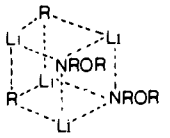
The suggestion of an S_N2-like reaction between an organolithium reagent and a lithium alkoxyamide requires a close ap-

(30) See: Pross, A. *Acc. Chem. Res.* **1985**, *18*, 212 for discussion.
(31) See: Russel, G. A.; Ros, F.; Hershberger, J.; Tashtoush, H. *J. Org. Chem.* **1982**, *47*, 1480.

proach between two formal anions. It is well-known that lithium species are highly aggregated, and there have been many suggestions of a role for aggregated lithium species on reaction pathways.[32] Two possibilities for the present reaction, modeled after the dimer and tetramer structures established for organolithium reagents, are shown as **27** and **28**. In both complexes



27



28

the nucleophilic carbon is positioned such that it could move into a trajectory which would allow backside displacement with the σ^* orbital of the nitrogen oxygen bond. In this simple rationale the formal negative charge at nitrogen can be seen to favor the sp^3 to sp^2 transformation of that atom, and the contracted orbitals should provide a tighter transition state. The tetramer model **28** may have an advantage over **27** in that the developing alkoxide is nearer a formally positive lithium. On the other hand in fluid solution external lithium ions could be involved. The central postulate is that lithium bridging promotes reaction between two species which would normally be considered to repel each other.

Following our initial report of these displacements, three theoretical papers have appeared on this reaction. Boche[33] and Armstrong[34] have calculated structures for derivatives of **27**, and McKee[35] has calculated reaction pathways for the conversion of **27** to product. All results are consistent with the importance of lithium bridging. However McKee's work suggests that the reaction proceeds via a trigonal bipyramid with lithium at the axial position. The intermolecularity observed in our earlier case in which a five-membered ring would be required for intramolecular reaction[18] is attributed to differences in the stability of the reactant complex, with barriers of 44.9 and 47.2 kcal/mol calculated for the inter- and intramolecular reactions in that case. We do not know if the relative heights of these gas-phase barriers would be appreciably affected by the potential six-membered ring of the present case, but it is clear the heights of the calculated barriers are far above those of a reaction which proceeds at −15 °C in solution. The calculations may also reflect the need for the ions to be strongly associated in the gas phase. We do not doubt the many advantages of calculations in this area; however, in view of the above uncertainties, our inclination is to prefer the analogy of the S_N2 reaction and to expect solvent to play a major role in association with the lithium ions.

Restriction of the geometry of a reaction by probing its confinement to a ring is a general approach which has been used by Eschenmoser to investigate nucleophilic displacement at carbon,[26] by Baldwin for generalizations about ring closure reactions,[29] and by Kampmeier to study radical displacement at sulfur.[36] We wish to note that this approach to determining the geometry of reactions at nonstereogenic atoms should be widely applicable. The possibility of defining a reaction trajectory by investigating intra- and intermolecularity as a function of ring size is particularly interesting.[37,38]

In summary the present work provides a novel and efficient method for the amination of organolithium reagents. We provide evidence that this formal displacement proceeds through a transition state in which the entering and leaving groups prefer specified geometry, presumably that of an S_N2 processes, by extension of an approach which should be widely applicable. This novel reaction may be considered another example of a complex induced proximity effect whereby juxtaposition between reactive groups in a metal substrate complex promotes a novel reaction.[39]

Experimental Section[40]

All glassware was oven-dried (150 °C) and cooled under a nitrogen atmosphere. Diethyl ether (ether) was dried by distillation from lithium aluminum hydride and stored under a nitrogen atmosphere. Hexane and pentane were dried by refluxing over 3 Z sieves for 4 h followed by distillation onto 3 Z sieves. Tetrahydrofuran (THF) was dried by distillation of Aldrich Gold Label material under a nitrogen atmosphere from sodium/benzophenone ketyl radical. Tetramethylethylenediamine (TMEDA) was distilled from calcium hydride and stored under a nitrogen atmosphere. Solvents were stored under a nitrogen atmosphere. Unless otherwise indicated, organolithium reagents were titrated according to the method of Tischler[41] or with weighted amounts of 1,3-diphenyl-2-propanone *p*-tosylhydrazone[42] in THF at 0 °C. Grignard reagents were titrated by back titration with standardized sodium hydroxide solutions. Unless otherwise stated, the organometallic reagents used were obtained commerically and stored at room temperature under a nitrogen atmosphere. *sec*-Butyllithium and *tert*-butyllithium were stored in bottles at −10 °C over indicating Drierite in a closed container. Pyridine–borane-d_3 was prepared according to a previously published procedure by using sodium borodeuteride (98 atom % D).[43]

Methoxyamine (1),[44] A paste of 0.24 mol of sodium hexyloxide was prepared by treatment of 13 g (0.24 mol) of sodium hydride (50% oil dispersion) with 100 mL of hexanol at −5 °C under a nitrogen atmosphere. Then 20 g (0.24 mol) of methoxyamine hydrochloride was added, and after the reaction had subsided, the mixture was fractionally distilled through a column, which was half filled with glass helices and half filled with sodium hydroxide pellets, to give 6.5 g (57%) of **1** as a clear colorless liquid: bp 47–48 °C (lit.[45] bp 48 °C); ^{1}H NMR δ 5.4 (br s, 2 H), 3.5 (s, 3 H).

***N*-Methylmethoxyamine (9)**, To a stirred solution of 6.05 g (0.06 mol) of commercially available *N*-methylmethoxyamine hydrochloride in 20 mL of 50% methanol at −10 °C were added 3.6 g of potassium hydroxide (85%) pellets. The mixture was fractionally distilled through a column of sodium hydroxide pellets to give 2.5 g (68%) of **9** as a clear colorless liquid: bp 42 °C (lit.[45] bp 42 °C); ^{1}H NMR δ 5.6 (br s, 1 H), 3.5 (s, 3 H), 2.7 (s, 3 H).

Acetophenone *O*-Methyloxime, A stirred solution of 5.0 g (0.04 mol) of acetophenone, 4.0 g (1.2 equiv) of methoxyamine hydrochloride, and 15 mL of pyridine in 100 mL methanol was refluxed overnight and then

(32) For recent work in a variety of systems: Streitweiser, A. *Acc. Chem. Res.* **1984**, *17*, 313. Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255. Jackman, L. M.; Scarmoutzos, L. M. *J. Am. Chem. Soc.* **1984**, *106*, 4627. Amstutz, R.; Laube, T.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1984**, *67*, 224. Arnett, E. M.; Maroldo, S. G.; Schriver, G. W.; Schilling, S. L.; Troughton, E. B. *J. Am. Chem. Soc.* **1985**, *107*, 2091. Buese, M. A.; Hogen-Esch, T. E. *J. Am. Chem. Soc.* **1985**, *107*, 4509. Al-Aseer, M. A.; Allison, B. D.; Smith, S. G. *J. Org. Chem.* **1985**, *50*, 2715. McGarrity, J. F.; Ogle, C. A.; Brich, Z.; Loosli, H. R. *J. Am. Chem. Soc.* **1985**, *107*, 1810. Kaufmann, E.; Schleyer, P. V. R.; Houk, K. N.; Wu, Y. D. *J. Am. Chem. Soc.* **1985**, *107*, 5560.

(33) Boche, G.; Wagner, H. U. *J. Chem. Soc., Chem. Commun.* **1984**, 1591.

(34) Armstrong, D. R.; Smith, R.; Walker, G. T. *J. Chem. Soc.*, **1985**, 789.

(35) McKee, M. L. *J. Am. Chem. Soc.* **1985**, *107*, 859.

(36) Kampmeier, J. A. *ACS Symp. Ser.* **1978**, *69*, 275. See, also: Drury, R. F.; Kaplan, L. *J. Am. Chem. Soc.* **1972**, *94*, 3982 for an early suggestion of this approach.

(37) King, J. F.; McGarrity, M. J. *J. Chem. Soc., Chem. Commun.* **1982**, 175.

(38) For a recent discussion of reaction trajectories and intramolecularity, see: Menger, F. M. *Acc. Chem. Res.* **1985**, *18*, 128.

(39) This effect has been noted in a number of reactions of organolithium compounds for examples, see: Gschwend, H. W.; Rodriquez, H. R. *Org. React. (NY)* **1979**, *26*, 1. Vara Prasad, J. V. N.; Pillai, C. N. *J. Organomet. Chem.* **1983**, *259*, 1. Beak, P.; Hunter, J. E.; Jun, Y. M. *J. Am. Chem. Soc.* **1983**, *105*, 6350. Meyers, A. I.; Pansagrau, P. D. *Tetrahedron Lett.* **1984**, *25*, 2941. Klumpp, G. W. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 1.

(40) Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained in deuteriochloroform unless otherwise indicated; chemical shifts are reported in δ (ppm) downfield from an internal tetramethylsilane standard. Mass spectral data were obtained by M. C. Cook and associates on Varian MAT-CH5 and 731 mass spectrometers. Elemental analyses were performed by Mr. J. Nemeth and associates. Melting points are uncorrected. Boiling points were recorded during distillations and are uncorrected. Unless otherwise stated, isotope ratio mass spectral data were obtained by examination of the molecular ion region with field ion (FI) mass spectrometry and a multichannel signal averager (msa).

(41) Tischler, A. N.; Tischler, M. H. *Aldrichimica Acta* **1978**, *11*, 20.

(42) Lipton, M. F.; Sorensen, C. M.; Sadler, A. C.; Shapiro, R. H. *J. Organomet. Chem.* **1980**, *186*, 155.

(43) Taylor, M. D.; Grant, L. R.; Sands, C. A. *J. Am. Chem. Soc.* **1955**, *77*, 1506.

(44) This procedure was developed by Dr. J. Lawson of Monsanto, St. Louis, MO.

(45) Bissot, T. C.; Parry, R. W.; Campbell, D. H. *J. Am. Chem. Soc.* **1957**, *79*, 796. *Handbook of Chemistry of Physics*, 55th ed.; Weast, R., Ed.; The Chemical Rubber Co.: Cleveland, OH, 1974; p C-515. Adams, R.; French, H. E. *J. Am. Chem. Soc.* **1921**, *43*, 651.

evaporated. Extractive workup with ether provided a liquid which was distilled in a Kugelrohr apparatus with a hot air bath to give 5.13 g (86%) of acetophenone-*O*-methoxime as a clear colorless liquid: ^{1}H NMR δ 7.5, 7.2 (m, 5 H), 3.9 (s, 3 H), 2.2 (s, 3 H); IR (cm^{-1}) 3000 (m), 1640 (w), 1600 (w), 1520, 1490, 1480, 1385, 1325, 1200, 1100, 1080, 1000, 900, 785, 770, 700. Anal. Calcd for $C_9H_{11}NO$: C, 72.44; H, 7.44; N, 9.39. Found: C, 72.32; H, 7.60; N, 9.49.

***N*-Methoxy-*N*-(1-phenylethyl)amine (4).** To a stirred solution of 1.0 g (0.007 mol) of acetophenone-*O*-methyloxime and 2 mL (3.3 equiv) of pyridine–borane complex in 10 mL of ethanol at −10 °C was added slowly 20 mL of 10% hydrogen chloride dropwise. The mixture was stirred for 10 min at room temperature, and anhydrous sodium carbonate was added. Extractive workup with chloroform gave a liquid which was distilled in a Kugelrohr apparatus with a hot air bath to give 0.87 g (86%) of **4** as a clear colorless liquid: ^{1}H NMR δ 7.2 (s, 5 H), 5.5 (br s, 1 H), 4.1 (q, 1 H), 3.4 (s, 3 H), 1.3 (d, 3 H); IR (cm^{-1}) 3330 (w), 3000 (s), 1640 (w), 1520, 1480, 1380, 1155, 1080, 1040, 1020, 950, 830, 755, 690. Anal. Calcd for $C_9H_{13}NO$: C, 71.47; H, 8.67; N, 9.27. Found: C, 71.31; H, 8.62; N, 9.21.

***O*-(2-Bromoethyl) *N*-(1-Phenylethyl)-*N*-methoxycarbamate (8).** To 0.420 g (0.0027 mmol) of **4** and 2 mL of triethylamine in dry methylene chloride was added 0.298 mL (0.0027 mmol) of bromoethyl chloroformate. The solution was stirred 12 h at room temperature, diluted with methylene chloride, extracted with 10% HCl and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the solvent gave 0.688 g (89.1%) of **8**: ^{1}H NMR δ 7.22 (m, 5 H), 5.12 (q, 1 H), 4.32 (t, 2 H), 3.4–3.5 (m, 5 H), 1.6 (d, 3 H).

***N*-Methoxy-*N*-[-2-(*o*-bromophenyl)ethyl]amine (17).** To a solution of 5.4 g (0.03 mol) of *o*-bromobenzyl cyanide in 34 mL of ether cooled to just before freezing was added slowly dropwise 34 mL (1.2 equiv) of a 1 M solution of diisobutylaluminum hydride (DIBAL) in hexane. The mixture was stirred at room temperature for 24 h and poured into 50 mL of saturated ammonium chloride solution. Extractive workup with ether provided the crude aldehyde, which was dissolved in 100 mL of methanol, and 18 mL of pyridine and 2.8 g of methoxyamine hydrochloride were added. The mixture was refluxed overnight and evaporated. Extractive workup with ether provided a liquid which was distilled in a Kugelrohr apparatus with a hot air bath to give 2.49 g (39%) of the oxime as a clear colorless liquid: ^{1}H NMR δ 7.4, 7.3–7.0, 6.7 (m, 5 H), 3.9, 3.8 (s, 3 H), 3.75, 3.6 (d, 2 H); IR (cm^{-1}) 3000 (m), 1650 (w), 1600 (w), 1500, 1460, 1100, 1050, 890, 760. Anal. Calcd for $C_9H_{10}NOBr$: C, 47.37; H, 4.42; N, 6.14; Br, 35.05. Found: C, 47.03; H, 4.28; N, 6.08; Br, 35.39.

To a solution of 1 g (0.0044 mol) of the above oxime and 1.5 mL (3.3 equiv) of pyridine–borane complex in 6 mL of ethanol at −5 °C was slowly added dropwise 12 mL of 10% aqueous hydrogen chloride. The mixture was stirred at room temperature for 10 min and basified with anhydrous sodium carbonate. Extractive workup with ether gave a liquid which was distilled in a Kugelrohr apparatus with a hot air bath to give 0.95 g (94%) of **17** as a clear colorless liquid: ^{1}H NMR δ 7.5, 7.1 (d, m, 4 H), 5.4 (br s, 1 H), 3.5 (s, 3 H), 3.0 (m, 4 H); IR (cm^{-1}) 3290 (w), 2950 (m), 1580 (w), 1480, 1450, 1080, 1040, 950, 810, 755. Anal. Calcd for $C_9H_{12}NOBr$: C, 46.95; H, 5.26; N, 6.09; Br, 34.74. Found: C, 47.03; H, 5.15; N, 6.05; Br, 34.65.

***N*-Methyl-*N*-[2-(*o*-bromophenyl)ethoxy]amine (19).** To 5.75 g (0.15 mol) of lithium aluminum hydride in 150 mL of anhydrous ether, with stirring, under a nitrogen atmosphere, was added, in 1.5 h, a solution of 22.58 g (0.105 mol) of (2-bromophenyl)acetic acid in 250 mL of anhydrous ether. The mixture was subsequently heated under reflux for 40 min, cooled, treated with 10 mL of ethyl acetate, and then poured on 0.75 kg of crushed ice. Following the addition of 200 mL of 20% aqueous hydrochloric acid, the product alcohol was isolated by ether extraction to give 20.08 g (~95%) of pale yellow oil, which was characterized by IR and used without further purification.

A solution of 1.85 g (9.2 mmol) of the above alcohol, 1.5 g (9.2 mmol) of *N*-hydroxyphthalimide, 2.4 g (9.2 mmol) of triphenylphosphine, and 1.8 g (1.1 equiv) of diethyl azodicarboxylate (DEAD) in 60 mL of THF was stirred at room temperature for 24 h and evaporated to give a crude yellow solid which was recrystallized from methanol to give 2.5 g (78.5%) of *N*-[(2-bromophenethyl)oxy]phthalimide as a white glass-wool-like solid: mp 110–111 °C; ^{1}H NMR δ 6.96–7.8 (m, 8 H), 4.4 (t, 2 H, J = 7.0 Hz), 3.3 (t, 2 H, J = 7.0 Hz); IR (cm^{-1}) 1780 (w), 1720 (s), 1180 (m), 1128 (m), 985, 878, 758, 695. Anal. Calcd for $C_{16}H_{12}BrO_3N$: C, 55.49; H, 3.47; N, 4.05; Br, 23.12. Found: C, 55.49; H, 3.47; N, 4.00; Br, 23.06.

A solution of 4.3 g (12.43 mmol) of the above phthalimide and 1.65 g (85%) of hydrazine hydrate in 200 mL of ethanol was refluxed for 2 h and evaporated, and 200 mL of ether and 200 mL of 40% potassium hydroxide were added. The aqueous layer was extracted 5 times with ether, and the ether layers were combined. Then the ether was extracted by 10% aqueous hydrochloric acid 3 times. The aqueous layers were combined and neutralized by potassium hydroxide, extracted 5 times with ether, dried over anhydrous potassium carbonate, filtered, and evaporated under reduced pressure to give 1.3 g (48.4%) of [2-(-*o*-bromophenyl)-ethoxy]amine, a colorless liquid, which was used in the next reaction without further purification: ^{1}H NMR δ 6.8–7.6 (m, 4 H), 5.3 (br, 2 H), 3.8 (t, 2 H, J = 6 Hz), 2.95 (t, 2 H, J = 6 Hz); IR (cm^{-1}) 3320 (w), 2920 (w), 2860 (w), 1585 (m), 1470, 1440, 1370, 1160, 1025, 750.

To a solution of 1.3 g (0.006 mol) of the above amine in 6 mL of ethanol at −10 °C under a nitrogen atmosphere were added 0.5 g (~1 equiv) of a 37% solution of formaldehyde in water, dissolved in 6 mL of ethanol, and 2 mL of pyridine–borane complex. The mixture was stirred at room temperature for 3 h and cooled to −10 °C, and then 18 mL of 10% aqueous hydrochloric acid was added dropwise. The mixture was stirred at room temperature for 12 h and basified with anhydrous sodium carbonate. Extractive workup with ether provided a liquid which was purified on a Chromatotron by using 30% ethyl acetate in hexane as eluent to give 0.6061 g (43.9%) of **19** as a clear colorless liquid: ^{1}H NMR δ 6.9–7.5 (m, 4 H), 3.87 (t, 2 H, J = 7 Hz), 3.0 (t, 2 H, J = 7 Hz), 2.7 (s, 3 H); IR (cm^{-1}) 2960 (m), 2880 (m), 1475 (m), 1440 (m), 1370, 1205, 1035, 950, 760. Anal. Calcd for $C_8H_{10}NOBr$: C, 44.45; H, 4.67; n, 6.48; Br, 37.00. Found: C, 44.37; H, 4.85; N, 6.67; Br, 37.30.

Preparation of 19-d_2 and 19-d_3. To 5.75 g (0.15 mol) of lithium aluminum deuteride (99 atom % D) in 150 mL of anhydrous ether, with stirring, under a nitrogen atmosphere, was added, in 1.5 h, a solution of 22.58 g (0.105 mol) of 2-bromophenylacetic acid in 250 mL of anhydrous ether. Reaction as described above gave 19.68 (93.5%) of 2-(*o*-bromophenyl)-1,1-dideuterioethanol as a colorless oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.0–7.6 (m, 4 H), 3.0 (s, 2 H), 1.9 (s, 1 H); IR (cm^{-1}) 3800 (br), 3025 (w), 29.60 (w), 2200 (w), 2100 (w), 1560 (s), 1465 (m), 1435 (m), 1100, 1090, 1018, 955, 970, 745, 650.

A solution of 4.30 g (0.022 mol) of the above alcohol, 3.62 g (0.022 mol) of *N*-hydroxyphthalimide, 5.8 g (0.22 mol) of triphenylphosphine, and 4.3 g (0.024 mol) of diethyl azodicarboxylate was treated as described above to give 5.9 g (76.4%) of 2-(*o*-bromophenyl)-1,1-dideuterioethoxyphthalimide as a white glass-wool-like solid: mp 110–111 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.0–7.9 (m, 8 H), 3.25 (s, 2 H); IR (cm^{-1}) 3042 (s), 1788 (s), 1734 (s), 1244 (m), 1225 (m), 1179 (s), 1129 (s), 1075 (m), 1026 (m), 988 (s), 876, 820, 758, 785.

A solution of 5.0 g (0.014 mol) of the above phthalimide and 2.4 g (0.075 mol) of anhydrous hydrazine was treated as above to give 2.66 g (87.2%) of 2-(*o*-bromophenyl)-1,1-dideuterioethoxyamine as a colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.0–7.6 (m, 4 H), 5.4 (s, 2 H), 3.0 (s, 2 H); IR (cm^{-1}) 3300 (br), 3050 (w), 2920 (w), 2860 (w), 2200 (w), 2100 (w), 1590 (w), 1560 (w), 1465 (m), 1435 (m), 1100, 1090, 1008, 970, 955, 745, 650.

To a solution of 1.3 g (0.006 mol) of the 2-(*o*-bromophenyl)-1,1-dideuterioethoxyamine in 6 mL of ethanol at −10 °C under a nitrogen atmosphere was added 0.5 g (0.006 mol) of a 37% solution of formaldehyde in water. Reduction with pyridine–borane-d_3 as described above gave 0.78 g (56.4%) of **19-d_2** and **19-d_3**: ^{1}H NMR (200 MHz, $CDCl_3$) 7.0–7.6 (m, 4 H), 5.1 (br, s, 1 H), 3.05 (s, 2 H), 2.7 (s, 2.2 H); MS, *m/e* (area) (FI) 229 (310), 230 (366), 231 (5563), 232 (17141); MS, for unlabeled compound 228 (354), 229 (M^+, 12/22), 230 (4603), 231 (14291), 232 (4071); IR (cm^{-1}) 3280 (w), 3070 (w), 2960 (s), 2875 (s), 1470 (s), 1440 (s), 1370 (w), 1205 (w), 1040, 950, 875, 755, 660.

General Procedure for the Amination of Organolithiums with Methyllithium–Methoxyamine. To a stirred solution of 2 equiv of methyllithium in ether at −78 °C under a nitrogen atmosphere was added dropwise a solution of 2 equiv of methoxyamine (**2**) in hexane. The 1 equiv of the organolithium was added all at once, and the mixture was warmed to −15 °C for 2 h and quenched with water. In the case of volatile amine products, pyridine and benzoyl chloride were then added, and the mixture was stirred overnight. Extractive workup with chloroform provided a crude product which was purified by mplc. The benzamide was purified either by distillation in a Kugelrohr apparatus with a hot air bath or dried under a vacuum. The yield of the amide is based on moles of organolithium. Representative cases will be given.

Amination of Ethyllithium obtained with 2 equiv of methyllithium–methoxyamine with 12.8 mL (.0106 mol) of a 0.83 M solution of methyllithium in ether, 0.5 g (0.0106 mol) of **2** in 10 mL of hexane, 8.1 mL (0.0053 mol) of a 0.66 M solution of ethyllithium, 0.5 mL of water, 10 mL of pyridine, and 2.3 mL of benzoyl chloride. Chromatography using ethyl acetate in hexanes gave 0.62 g (78%) of *N*-ethylbenzamide as a white solid: mp 68–69 °C (lit.[46] mp 68–69 °C); ^{1}H NMR δ 7.8 (dd, 2 H), 7.5–7.2 (m, 3 H), 6.4 (br s, 1 H), 3.5 (p, 2 H), 1.2 (t, 3 H).

Amination of *n*-Butyllithium obtained with 1 equiv of methyllithium–*N*-(1-phenylethyl)methoxyamine with 1.3 mL (0.0015 mol) of a 1.17 M solution of methyllithium in ether, 0.23 g (0.0015 mol) of **4** in 5 mL of

(46) Oliveri-Mandala, E. *Gazz. Chim. Ital.* **1914**, *44*, 669.

hexane, 1.0 mL (0.0015 mol) of a 1.51 M solution of *n*-butyllithium in hexane, warmed to 40 °C for 2 h, and followed by 1 mL of water gave 0.180 g (68%) of *N*-*n*-butyl-*N*-(1-phenylethyl)amine as a clear colorless oil: ^{1}H NMR δ 7.1, 6.5 (m, m, 5 H), 3.4 (q, 1 H), 3.2 (br s, 1 H), 1.3, 1.1, 0.8 (br m, d, br t, 12 H); IR (cm^{-1}) 3350 (w), 3000 (s), 1600 (s), 1500, 1460, 1440, 1375, 1320, 1260, 1180, 1155, 1000, 870, 750, 690. Anal. Calcd for $C_{12}H_{19}N$: C, 81.28; H, 10.81; N, 7.91. Found: C, 80.90; H, 10.74; N, 7.76.

Amination of *n*-Butyllithium with 8. To 106 g (0.35 mmol) of the carbamate **8** dissolved in dry hexane and cooled to −78 °C was added 0.35 mL (2.18 M, 2.2 equiv, 0.77 mmol) of *tert*-butyllithium. The solution was warmed to room temperature, stirred for 3 h, recooled to −40 °C, treated with *n*-BuLi (0.2 mL, 2.06 M, 1.2 equiv), and heated at 40 °C for 2 h. Extractive workup provided 40 mg (64.5%) of *N*-*n*-butyl-*N*-(1-phenylethyl)amine.

***N*-Acetylindoline from 17.** To a stirred 1.9 mL (0.0022 mol) sample of a 1.17 M solution of methyllithium in ether at −78 °C under nitrogen was added dropwise 0.5 g of **17** in 10 mL of hexane followed by 1.5 mL (0.0022 mol) of a 1.51 M solution of *n*-butyllithium in hexane. The mixture was stirred for 15 min, warmed to −15 °C for 3 h, and quenched with 0.5 mL of water. Then 120 mL of ether, 1 mL of pyridine, and 0.9 mL of acetyl chloride were added, and the mixture was stirred overnight. Extractive workup with chloroform provided an oil which was chromatographed on a silica gel column by using 70% ethyl acetate in hexanes as eluant to give 0.28 g (78%) of *N*-acetylindoline as a white solid (mp 85–95 °C). Recrystallization from hexane gave 0.15 g (42%) of white needles: mp 102–104 °C (lit.[47] mp 105 °C); ^{1}H NMR δ 8.2 (d, 1 H), 7.1 (m, 3 H), 4.0 (t, 2 H), 3.1 (t, 2 H), 2.2 (s, 3 H).

20 and 21 from 19. To a stirred 1.0 mL (0.0013 mol) sample of a 1.3 M solution of methyllithium in ether at −78 °C under a nitrogen atmosphere was added dropwise 0.289 g (0.0013 mol) of **19** in 6 mL of hexane followed by 2.2 mL (0.0026 mol) of a 1.2 M solution of *tert*-butyllithium in pentane. The mixture was stirred for 30 min and warmed to −15 °C for 2 h, then 20 mL of ether was added, the mixture was cooled to −78 °C, 0.1 mL of water and 1 mL (≃ 10 equiv) of acetyl chloride were added consequently, and the mixture was stirred at room temperature for 48 h and evaporated. Extractive workup with chloroform provided an oil which was purified by mPLC using 75% ethyl acetate in hexane as eluent to give 22 mg (7.2%) of **20** as a pale yellow oil, 38 mg (11.5%) of **21** as a pale yellow oil, and 161 mg (55%) of 2-phenylethyl acetate as a colorless liquid, identified by its NMR spectra.

20: ^{1}H NMR (20 MHz, $CDCl_3$) δ 7.1–7.4 (m, 4 H), 4.3 (t, 2 H, J = 7.0 Hz), 3.2 (s, 3 H), 2.9 (t, 2 H, J = 7.0 Hz), 2.0 (s, 3 H), 1.8 (s, 3 H); IR (cm^{-1}) 3460 (br), 2960 (m), 1740 (s), 1650 (s), 1490 (m), 1430 (m), 1370 (s), 1230 (s), 1140, 1035, 0770, 750. MS (CH-5), *m/e* (area) 235 (M$^+$, 654), 220 (122), 183 (756), 175 (1277). Anal. Calcd for $C_{11}H_{15}NO_2$: C, 68.36; H, 7.84; N, 7.25. Found: C, 67.98; H, 7.89; N, 7.29.

21: ^{1}H NMR δ 7.1–7.4 (m, 5 H), 4.0 (t, 2 H, J = 7.0 Hz), 3.1 (s, 3 H), 2.9 (t, 2 H, J = 7.0 Hz), 1.9 (s, 3 H); IR (cm^{-1}) 3500 (br), 3005 (w), 2910 (w), 2860 (w), 1640 (s), eq 1370 (m), 1170, 1010, 965, 840, 735, 690. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.35; H, 7.30; N, 5.95. Found: C, 66.56; H, 7.33; N, 5.92.

20/20-d_1/20-d_2/20-d_3 and 21/21-d_2/21-d_3 from 19, 19-d_2 and 19-d_3. To a 1.40-mL (0.0018 mol) sample of 1.3 M solution of methyllithium in ether at −78 °C under a nitrogen atmosphere were added slowly dropwise 0.2070 g (0.0009 mol) of **19** and 0.2100 g (0.0009 mol) of a mixture of **19-d_2/19-d_3** in 12 mL of hexane followed by 2.54 mL (0.0036 mol) of a 1.42 M solution of *tert*-butyllithium in pentane. The mixture was stirred for 30 min and warmed to −15 °C for 2 h, and 20 mL of ether was added. The mixture was cooled to −78 °C, and 1.4 mL (~5 equiv) of acetyl chloride was added, and the solution stirred at room temperature for 48 h and evaporated. Extractive workup with chloroform provided an oil which was purified by medium pressure liquid chromatography using 70% ethyl acetate in hexane as eluent to give 0.0435 g (10.1%) of a mixture of **20/20-d_1/20-d_2/20-d_3** and 0.0159 g (4.5%) of a mixture of **21/21-d_1/21-d_2/21-d_3**: ^{1}H NMR of the mixture of **20/20-d_1/20-d_2/20-d_3** (200 MHz, $CDCl_3$) δ 7.1–7.4 (m, 4 H), 4.3 (t, 1 H, J = 7.0 Hz), 3.2 (s, 2 H), 2.9 (m, 2 H), 2.0 (s, 3 H), 1.8 (s, 3 H) ^{1}H NMR of the mixture of **21/21-d_1/21-d_2/21-d_3** (200 MHz, $CDCl_3$) δ 7.2–7.4 (m, 5 H), 4.1 (t, 1 H, J = 7), 3.1 (s, 2 H), 2.9 (m, 2 H), 2.0 (s, 3 H). MS of the mixture of **20/20-d_1/20-d_2/20-d_3** (FI) *m/e* (area) 234 (86), 235 (170 060), 236 (110 832), 237 (175 804), 238 (108 375), 239 (12 856), 240 (1962); MS of **20** (FI) *m/e* (area) 234 (193), 235 (M$^+$, 858 456), 236 (118 954), 237 (8954); MS of the mixture of **21/21-d_1/21-d_2/21-d_3** (FI) *m/e* (area) 192 (148), 193 (20 061), 194 (3716), 195 (7116), 196 (20 811), 197 (3650), 198 (553); MS of **21** (FI) *m/e* (area) 192 (33), 193 (M$^+$, 51 726), 194 (6583), 195 (635), 196 (286).

Acknowledgment. We are grateful to the National Institutes of Health and the National Science Foundation for support of this work. The advice and assistance of Dr. S. G. Mills is particularly appreciated, and we are grateful to Dr. J. Lawson for disclosure of results.

Registry No. 1, 100859-25-4; **4**, 103794-57-6; **8**, 103794-58-7; **9**, 1117-97-1; **17**, 86296-00-6; **17** (*O*-methyl oxime derivative), 86296-01-7; **19**, 103794-59-8; **19-d_2**, 103794-61-2; **19-d_3**, 103794-62-3; **20**, 103794-67-8; **20-d_1**, 103794-69-0; **20-d_2**, 103794-70-3; **20-d_3**, 103794-71-4; **21**, 103794-68-9; **21-d_2**, 103794-72-5; **21-d_3**, 103794-73-6; C_2H_5Li, 811-49-4; $C_2H_5NHCOC_6H_5$, 614-17-5; *n*-$C_4H_9NHCOC_6H_5$, 2782-40-3; *s*-$C_4H_9NHCOC_6H_5$, 879-71-0; *t*-$C_4H_9NHCOC_6H_5$, 5894-65-5; $C_6H_5CH_2NHCOC_6H_5$, 1485-70-7; CH_2=$CHCH_2NHCOC_6H_5$, 10283-95-1; $C_6H_5NHCOC_6H_5$, 93-98-1; $CH_3NHCOC_6H_5$, 613-93-4; *o*-$CH_3C_6H_4NHCOC_6H_5$, 584-70-3; *n*-C_4H_9Li, 109-72-8; *sec*-C_4H_9Li, 598-30-1; *t*-C_4H_9Li, 594-19-4; $C_6H_5CH_2Li$, 766-04-1; CH_2=$CHCH_2Li$, 3052-45-7; C_6H_5Li, 591-51-5; *o*-$CH_3C_6H_4Li$, 6699-93-0; *o*-CON(*i*-Pr)$_2C_6H_4Li$, 62924-96-3; *o*-CON(*i*-Pr)$_2C_6H_4NH_2$, 103794-66-7; *n*-$C_4H_9NCH_3COC_6H_5$, 79242-10-7; *sec*-$C_4H_9NCH_3COC_6H_5$, 86295-99-0; *t*-$C_4H_9NCH_3COC_6H_5$, 49690-12-2; $C_6H_5NCH_3COC_6H_5$, 1934-92-5; sodium hexyloxide, 19779-06-7; sodium hydride, 7646-69-7; hexanol, 111-27-3; methoxyamine hydrochloride, 593-56-6; *N*-methylmethoxyamine hydrochloride, 6638-79-5; acetophenone *o*-methyloxime, 3376-33-8; acetophenone, 98-86-2; *o*-bromobenzyl cyanide, 19472-74-3; (2-bromophenyl)acetic acid, 18698-97-0; *N*-hydroxyphthalimide, 524-38-9; *N*-[(2-bromophenethyl)oxy]phthalimide, 91523-93-2; hydrazine, 302-01-2; [2-(*o*-bromophenyl)ethoxy]amine, 103794-60-1; formaldehyde, 50-00-0; 2-(*o*-bromophenyl)-1,1-dideuterioethanol, 103794-63-4; 2-(*o*-bromophenyl)-1,1-dideuterioethoxyphthalimide, 103794-64-5; 2-(*o*-bromophenyl)-1,1-dideuterioethoxyamine, 103794-65-6; 4-dibenzothiophenyllithium, 75288-58-3; 4-aminodibenzothiophene, 72433-66-0; *N*-*n*-butyl-*N*-(1-phenylethyl)amine, 5412-64-6; *N*-acetylindoline, 16078-30-1; bromoethyl chloroformate, 4801-27-8.

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