CH_2CH_2CO), 3.30–3.70 (m, 18 H, 4 ring CH_3 and 2 OCH_3), 4.30 (m, 4 H, CH_2CH_2CO), 9.35, 9.45 (each s, 1 H, 2,4-H), 9.70, 9.75 (each s, 1 H, meso H). UV-vis (CH_2Cl_2): λ_{max} 412 nm (ϵ 192000), 512 (13890), 544 (3930), 588 (3800), 654 (760). LR mass spectrum: *m/e* 606 (100), 572 (42), 533 (14), 499 (13). HR mass spectrum: calcd for $C_{32}H_{32}Cl_2N_4O_4$ 606.1801, found 606.1800.

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Displacements at the Nitrogen of Lithioalkoxylamides by Organometallic Reagents

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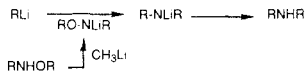
The conversions of *N*-(*o*-bromobenzyl)methoxylamine to *N*-acetylbenzoazetine (**1**), of *N*-[3-(*o*-bromophenyl)-*n*-propyl]methoxylamine to *N*-acetyltetrahydroquinoline (**2**), and of *N*-[4-(*o*-bromophenyl)-*n*-butyl]-methoxylamine to *N*-acetylbenzazapine (**3**) illustrate the use of this displacement reaction to form nitrogen-containing rings in an exocyclic reaction mode. An X-ray structural determination is reported for **1**. The formations of anilides by amination of aromatic organolithium reagents with lithium methoxylamide is also reported. Lithium reagents are found to be more effective than Grignard, copper, or zinc reagents in these displacements, and the yields decrease as the size of the substituents around nitrogen increases. The endocyclic restriction test is used to show that this displacement on nitrogen cannot occur within the endocyclic confines of a seven-membered ring. A S_N2 reaction pathway in a lithium complex is considered to be supported by these results.

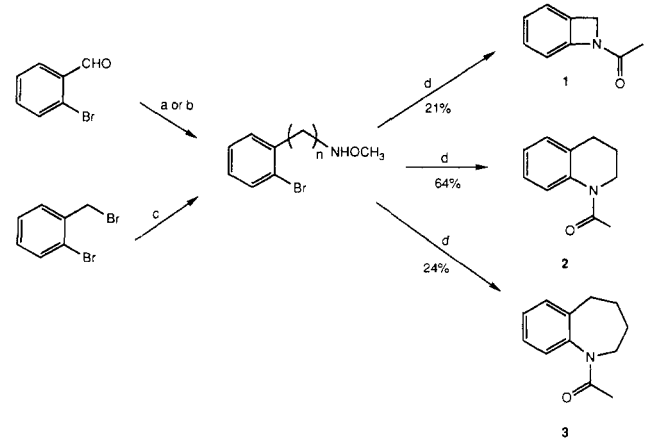
The formal displacement of an alkoxy group from an alkoxylamine, by an organolithium reagent, has been developed as a useful amination method.[1,2] Synthetically it has been shown that the species formed by lithiation of alkoxylamines and *N*-alkylalkoxylamines can aminate organolithium reagents. Mechanistically the endocyclic restriction test has been used to support our suggestion that the reaction occurs in an aggregated lithium complex of the reactants in which the entering and leaving groups are disposed at 180°.[3] In this paper we report synthetic uses of this amination, including a convenient preparation of a benzoazetine, and further investigation of the reaction mechanism.



Results and Discussion

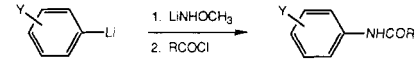
Cyclizations. This amination strategy can be used to form nitrogen-containing rings. The sequence which begins with the preparation of the appropriate (*o*-bromophenyl)alkanylmethoxylamine by straightforward methodology is illustrated by the synthesis of *N*-acetylbenzoazetine (**1**), *N*-acetyltetrahydroquinoline (**2**), and *N*-acetylbenzazapine (**3**). The key step is double lithiation of the aryl bromide to give an (*o*-lithiophenyl)alkyllithiomethoxylamide which then undergoes an exocyclic ring closure. Earlier we showed that indoline could be formed in this way, and in this work we have found that we could not prepare a benzazocine by this approach. This later failure is consistent with the slower rate of cyclization expected for an exocyclic ring closure of an eight-membered ring.[4]

Scheme I[a]



[a] (a) n = 1, NH_2OCH_3–HCl; BH_3–pyridine (78%); (b) n = 3, $Ph_3P{=}CHCO_2CH_3$; Mg, CH_3OH; DIBAL; NH_2OCH_3–HCl, BH_3–pyridine (39%); (c) $BrMgCH_2CH{=}CH_2$, BH_3–THF; H_2O_2, NaOH; oxallyl chloride, NH_2OCH_3–HCl; BH_3–pyridine (36%); (d) CH_3Li; t-C_4H_9Li; RCOCl.

Scheme II



4, Y = H, R = Ph (91%); **5**, Y = *p*-CH_3, R = Ph (93%); **6**, Y = *o*-C_2H_5, a mixture R = CH_3 (25%) and R v $CH_3CH{=}COCH_3$ (53%); **7**, Y = *o*-OCH_3, R = Ph (98%); **8**, Y = *m*-OCH_3, R = Ph (73%); **9**, Y = *p*-OCH_3, R = Ph (28%); **10**, Y = *m*-Cl, R = CH_3 (46%)

The structure of the benzoazetine **1** was assigned by standard methods, including vapor pressure osmometry, and confirmed by a single-crystal X-ray structure determination. The crystal structure for **1**, in space group P_{21c} with a = 9.529 (3) Å, b = 8.984 (2) Å, c = 9.439 (3) Å, β = 108.80 (2)°, Z = 4, was solved by direct methods and

(1) Sheverdina, N. I.; Kocheshkov, Z. *J. Gen. Chem. USSR* **1938**, *8*, 1825, appear to have been the first to observe this reaction.
(2) Beak, P.; Basha, A.; Kokko, B. J.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 1511 and references cited therein.
(3) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. This reaction, which formally brings together two negatively charged species for a bonding interaction, appears to be an example of the complex-induced proximity effect.
(4) Illuminate G.; Mandolini, L. *Acc. Chem. Res.* **1988**, *14*, 95. The slower cyclization presumably is then not competitive with the decomposition of the lithioalkoxyamide.

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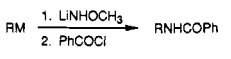
Scheme III



M = Li	R = *s*-Bu (68%), Ph (91%)
M = MgBr	R = *s*-Bu (19%), *n*-Bu (16%)
	R = Ph (37%, 54% 11 h)
M = RCuLi	R = *s*-Bu (58%), Ph (83%)
M = $(CH_3)_2ZnLi$	R = *s*-Bu (18%)

refined to $R = 0.040$ for 954 nonzero reflections recorded. The bond lengths of 1.35 Å between nitrogen and the carbonyl carbon and of 1.23 Å for the carbonyl group are consistent with a relatively normal amide functional group.[5] The *N*-methyl- and *N*-phenylbenzoazetines have been previously obtained by extrusion of sulfur dioxide and nitrogen from the appropriate precursors.[6,7] The present approach to the benzoazetine system appears to be the most convenient of the alternatives.

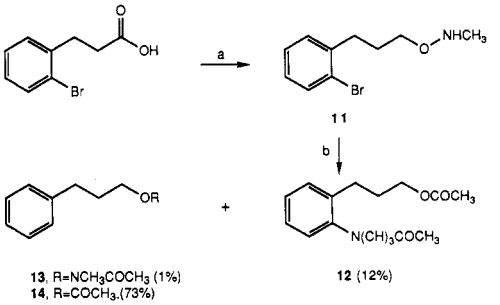
Aminations of Aromatic Lithium Reagents. We have carried out aminations of aromatic lithium reagents to give the products **4–10** as shown in Scheme II. The organolithium reagents were prepared from the corresponding aryl bromide or iodide, and the product lithioanilines were converted to amides for convenience in isolation. A range of substituents were used and a range of yields were obtained for the standard conditions of addition at −78 °C followed by warming to −15 °C for 2 h. These results suggest that this methodology is useful for amination of aromatic lithium reagents but that optimization of conditions may be necessary for each case.

Amination of Other Organometallic Reagents. In an effort to determine if other organometallic reagents would be more appropriate reagents for amination we have allowed representative Grignard, copper, and zinc reagents to react with lithium methoxylamide as shown in Scheme III. For comparison the yields of amides from *sec*-butyl- and phenyllithium are 68% and 91%, respectively. Examination of the data shows that only the *sec*-butyl- and phenylcopper reagents give yields comparable to the lithium reagents, and the Grignard and zinc reagents are less effective. From these results it appears that while other organometallic reagents can be aminated by a lithium alkoxylamide, the organolithium reagents are the most effective.

The Mechanism of Amination. We have previously used the endocyclic restriction test to show that the bond angles within five- and six-membered rings cannot accommodate the transition structure for the displacement at nitrogen in this amination reaction.[2] It would be expected that by variation in the size of the ring it might be possible to observe an endocyclic intramolecular reaction and thus an evaluation of the bond angles allowed in the transition structure could be obtained. We have probed this possibility by investigation of the lithiation of *N*-methyl-*O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine (**11**) in which an intramolecular concerted endocyclic transfer of nitrogen would occur in a seven-membered ring. The synthesis of **11** and the products of its lithiation **12–14** are shown in Scheme IV.

The intermediates in the formations of **12**, **13**, and **14** are shown as **15** and **16** (Scheme V). Initial deprotonation and bromine lithium exchange of **11** gives **15**, which is the precursor to **13**, and can lead to **14** by loss of the *N*-methyl group and protonation prior to acylation. The product **12** is the compound of interest to the question of transition-structure geometry. If the amination can proceed within a seven-membered endocyclic ring, the conversion of **15** to **12** should proceed in an intramolecular mode. If the amination cannot proceed within the confines of the bond angles of an endocyclic seven-membered ring, the conversion of **15** to **12** will be an intermolecular process.

Scheme IV[a]



[a] (a) BH_3; *N*-hydroxyphthalimide, NH_2NH_2, CH_2O, BH_3–pyridine (18%); (b) CH_3Li, 2 *t*-BuLi; CH_3COCl.

Scheme V

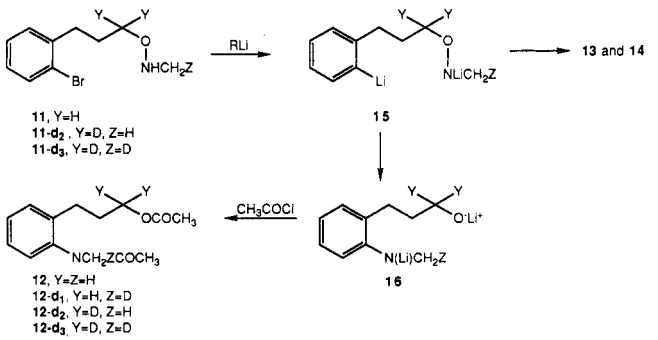


Table I. Deuterium Distributions for the Reaction of 11, 11-d_2, and 11-d_3 with Methyllithium and *tert*-Butyllithium

		percent[a]			
	entry	d_0	d_1	d_2	d_4
1[b]	11, experimental	53	0	1	35
	12, experimental	33	19	31	17
	12, intermolecular[e]	34	19	31	17
	12, intramolecular[e]	53	19	12	35
2[c]	11, experimental	60	0	10	30
	12, experimental	43	16	29	12
	12, intermolecular[e]	42	18	28	12
	12, intramolecular[e]	60	0	10	30
3[d]	11, experimental	59	0	11	30
	12, experimental	42	16	31	12
	12, intermolecular[e]	41	18	27	14
	12, intramolecular[e]	59	0	11	30

[a] Error is ±5%. [b] −78 to −15 °C over 3 h. [c] −78 to −15 °C over 1.5 h. [d] One-fourth the concentrations of above. [e] Calculated on the basis of the deuterium distribution of **11**.

Distinction between the inter- and intramolecular modes of reaction is achieved by the double-labeling experiment shown for **11** and **12** and summarized in Table I. The double-labeled 11-d_2 and 11-d_3 were obtained by use of deuterated reducing agents in the synthesis. The experiment was carried out by lithiation of mixtures of **11**, 11-d_2, and 11-d_3, and the products **12** and **14** were analyzed for distribution of the label.

$$11 + 11\text{-}d_2 + 11\text{-}d_3 \xrightarrow[\text{intermolecular}]{\text{RLi}} 12 + 12\text{-}d_1 + 12\text{-}d_2 + 12\text{-}d_3$$

(5) Surcouf, S. E.; Monan, J. P.; Malgrange, C. *Acta Crystallogr., Sect. B* **1978**, *34*, 2169, report values of 1.39 and 1.21 Å for *N*-acetyl-3-acetylindan. Pedersen, B. F. *Acta Chem. Scand.* **1967**, *21*, 1415, reports values of 1.33 and 1.26 Å for *N*-methylacetanilide.
(6) Smith, J. H.; Lancaster, M. *J. Chem. Soc., Chem. Commun.* **1980**, 471.
(7) Burgess, E. M.; McCullagh, L. *J. Am. Chem. Soc.* **1966**, *88*, 1580.

Table II. Yields of Dialkylbenzamides from the Reactions of *N*-Alkylmethoxyamines and Alkyllithium Reagents

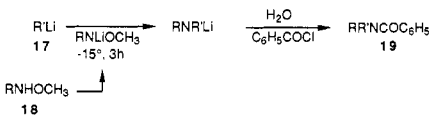
entry	17, R′	18, R	19, yield, %
1	*n*-Bu	Me	63[a,b]
2	*n*-Bu	*n*-Pr	64
3	*n*-Bu	*i*-Pr	47
4	*n*-Bu	1-phenylethyl	43
5	*n*-Bu	1-phenylethyl	68[b]
6	*s*-Bu	benzyl	19[a]

[a] Reaction allowed to warm to ambient temperature. [b] Reference 2.

The results calculated for the intramolecular and intermolecular modes of reaction are shown in Table I. It was found that **14** had the same deuterium distribution as the starting material while **12** has statistically distributed deuterium. Thus the first-formed lithium reagent **15**, which leads to **14**, does not scramble the deuterium label. However, **12**, the product of amination, has the deuterium label fully scrambled as shown by the three experiments in Table I.

Our conclusion is that the transfer of the *N*-methyl group to the carbon bearing lithium in **15** is an intermolecular process. The intermolecular reaction is preferred because the entering and leaving group are preferentially at 180° in the transition structure, and this angle cannot be achieved in the intramolecular mode in a seven-membered ring.

Effect of Substitution on Nitrogen. If the mechanism of the amination reaction is an S_N2-like processes it would be expected that the size of the alkyl substituent on nitrogen would have an effect on the reaction. The limited data we have on this point is summarized below for reactions of **17** and **18** providing **19** and in Table II. The first two entries, reactions of *N*-methylmethoxylamine and *N*-propylmethoxylamine, with *n*-butyllithium, show there to be little effect in the yield on replacement of the methyl by an *n*-propyl group. However comparison of these reactions with the third entry shows that of the reaction of isoproplymethoxylamine with *n*-butyllithium proceeds in lower yield. If the reaction is carried out under the standard conditions of −15 °C for 3 h followed by reaction with benzoyl chloride the product is *N*-isopropyl-*O*-methylbenzohydroxamic acid, indicating that no amination has occurred. However, when this reaction is warmed to room temperature for 14 h prior to the addition of benzoyl chloride, a 47% yield of amination product is observed. On the other hand when the substituent on nitrogen is the 1-phenylethyl group the amination of *n*-butyllithium proceeds in 43% yield at −15 °C, and in 68% yield at ambient temperature. Reaction of *sec*-butyllithium with *N*-benzylmethoxylamine gives amination in 19% yield. While comparisons of yields are less satisfactory for mechanistic comparisons than rates, it does appear that as the size of the groups around nitrogen increases the reaction is less effective.



These results are in accord with formation of an aggregated complex which leads by donation of the electrons from the carbanion into the σ^* orbital of the N–O bond to a transition structure which has the entering and leaving groups disposed at approximately 180°. Thus the seven-membered ring leading to **3** can be formed in an exocyclic mode, but the seven-membered ring required for an intramolecular endocyclic reaction is not accessible. Qualitatively, increasing the size of the substituent on nitrogen or of the formal nucleophilic center appears to reduce the yield of amination, consistent with this mechanism.

Summary. The present results further demonstrate that the amination of organolithium reagents by methoxylamines is a synthetically useful reaction. The mechanism of the reaction is consistent with reaction within a complex in an S_N2-like processes.

Experimental Section

General Procedures. ^1H NMR were recorded on either an EM-390 (90 MHz), an XL-200 (200 MHz), a QE-300(300 MHz), or a NT-360 (360 MHz) in $CDCl_3$, DMF-d_7, toluene-d_8, or DMSO-d_6 using tetramethylsilane (TMS) as the internal standard. ^{13}C NMR were recorded on an XL-200 (50 MHz) or a QE-300 (75 MHz) using $CDCl_3$ as the internal standard. Chemical shifts are reported in parts per million (ppm) relative to TMS. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broadened. Infrared spectra were recorded on a Perkin-Elmer 1320, an IBM IR/32 FT-IR, or a Nicolet 1320 spectrophotometer either neat, as a Nujol mull, or as a KBr pellet. Peaks are reported in cm^{-1} with the following relative intensities: s, strong; m, medium; w, weak. Mass spectra were performed on a Varian MAT CH-5 or 731 spectrometer with an ionization energy of 10 or 70 eV, or on a Hewlett-Packard 5890 gas chromatograph using a Hewlett-Packard 5970 mass-selective detector. Isotopic ratio mass spectral data were obtained from oscillographic traces of the molecular ion regions by the measurement of peak heights or by using computer-generated areas of the peaks. Deuterium incorporation was determined by the solution of a matrix in a program written by Chrisope.[8] Elemental analysis were performed by the University of Illinois Microanalytical Laboratory. Analytical thin-layer chromatography was performed on Merck silica gel plates with F-254 indicator. Visualization was accomplished by UV light, iodine, or phosphomolybdic acid. Medium-pressure liquid chromatography (MPLC) was performed using various silica gel columns containing Woehlm 32-63 silica gel. Chromatography using the Chromatotron was performed with either 1-, 2-, or 4-mm silica gel plates using 60 PF254 silica gel. High-pressure liquid chromatograph (HPLC) separations were performed on a Rainin Rabbit HPX HPLC on a Dynamax 21.4 mm × 25 cm silica column. Solvent systems were various mixtures of ethyl acetate (EtOAc)/hexane. Analytical gas chromatography was performed on a HP 5790A using a 25-m SC-52 capillary column. The injector temperature was 270 °C, and the detector temperature was 300 °C. The retention times were determined on a HP 3390A recorder. Melting points are uncorrected. Boiling points were obtained during bulb-to-bulb distillations using a Kugelrohr apparatus and are uncorrected.

Tetrahydrofuran (THF) and ethyl ether (Et_2O) were distilled from sodium/benzophenone. Hexane, toluene, xylene, methylene chloride (CH_2Cl_2), *sec*-butyl alcohol, methanol (CH_3OH), and pyridine were distilled from calcium hydride. *N*-(1-Phenylethyl)methoxylamine,[2] 4-(*o*-bromophenyl)-1-butene,[9] *o*-bromohydrocinnamic acid,[10] borane–pyridine-d_3 complex,[11] zinc chloride–TMEDA complex,[12] 1,2-benzo-3-azacyclooctane,[13] *N*-

(8) The amount of deuterium incorporation was determined by solving the following matrix equation:

$$\begin{bmatrix} I_0 \cdots I_{-1} \cdots I_{-n} \\ I_1 \cdots I_0 \cdots I_{-(n-2)} \\ \cdot \quad \cdot \quad \cdot \\ \cdot \quad \cdot \quad \cdot \\ I_n \cdots I_{n-1} \cdots I_0 \end{bmatrix} \begin{bmatrix} d_0 \\ d_1 \\ \cdot \\ \cdot \\ d_n \end{bmatrix} = a \begin{bmatrix} I'_{-1} \\ I'_0 \\ \cdot \\ \cdot \\ I'_{n-1} \end{bmatrix}$$

(9) Koppang, M.; Ross, G.; Woolsey, W.; Bartak, D. *J. Am. Chem. Soc.* **1986**, *108*, 1441.

(10) Meyers, A. I.; Temple, D. L.; Nolen, R. L.; Mihelich, E. D. *J. Org. Chem.* **1974**, *39*, 2778.

(11) Taylor, M. P.; Grant, L. R.; Sand, C. A. *J. Am. Chem. Soc.* **1967**, *89*, 5710.

(12) Kjonaas, R. A.; Watson, R. A. *Tetrahedron Lett.* **1986**, 1437. Kjonaas, R. A.; Vawter, E. J. *J. Org. Chem.* **1986**, *51*, 3993.

acetyl-1,2,3,4-tetrahydroquinoline,[14] and 1-benzazepine[13] were prepared by literature methods to give materials whose spectral data and/or physical data agreed with the reported values. Hexane and EtOAc for MPLC use were distilled over molecular sieves and potassium carbonate, respectively. *sec*-Butyl-, *n*-butyl-, *tert*-butyl-, and methyllithium solutions were titrated with *N*-benzylbenzamide as indicator.[15] Aromatic organolithium solutions were titrated using either 1,10-phenanthroline[16] or 1,3-diphenylacetone *p*-tosylhydrazone[17] as indicator. All other chemicals were used without further purification. Brine refers to a saturated sodium chloride solution, −15 °C refers to a methanol/ice bath, −40 °C refers to an acetonitrile/dry ice bath, and −78 °C refers to an isopropyl alcohol/dry ice bath. All reactions were performed under nitrogen and, when necessary, in oven-dried glassware.

***N*-(*o*-Bromobenzyl)methoxylamine.** To 2.62 g (14 mmol) of *o*-bromobenzaldehyde in 20 mL of methanol were added 2.60 g (31 mmol) of methoxylamine hydrochloride and 3 mL of pyridine. The solution was then heated at reflux overnight. The solution was cooled to 0 °C, and 2.78 g (30 mmol) of borane–pyridine complex was added. To this was added dropwise 30 mL of 10% HCl. After addition, the solution was allowed to stir at room temperature for 20 min. The reaction mixture was basified with Na_2CO_3 and extracted five times with Et_2O. The organic layer was then extracted five times with 10% HCl. The aqueous layer was basified and extracted five times with Et_2O, dried over sodium sulfate, and concentrated in vacuo. Distillation of the crude oil with a Kugelrohr apparatus gave a clear colorless liquid, 2.35 g (78%) of *N*-(*o*-bromobenzyl)methoxylamine: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.10–7.62 (m, 4 H, Ar*H*), 5.93 (br, 1 H, N*H*), 4.15 (s, 2 H, ArCH_2), 3.55 (s, 3 H, OCH_3); IR (neat, cm^{-1}) 3240 (m), 2940 (s), 2800 (m), 1460 (s), 1435 (s), 1040 (s), 915 (m), 745 (s), 650 (m).

Anal. Calcd for $C_8H_{10}NOBr$: C, 44.46; H, 4.66; N, 6.48; Br, 36.98. Found: C, 44.46; H, 4.68; N, 6.37; Br, 37.07.

***N*-Methyl-*O*-[3-(*o*-bromophenyl)propyl]hydroxylamine (11).** To 3.05 mL (0.024 mol) of 2,4,4-trimethyl-2-oxazoline in 100 mL of THF at −78 °C was added 17.9 mL (0.024 mol) of *n*-butyllithium. After 0.5 h at this temperature, 5.9 g (0.024 mol) of *o*-bromobenzyl bromide in 10 mL of THF was added. The solution was then warmed to room temperature. After 1 h at room temperature, the reaction was quenched with 5 mL of H_2O. The solvent was removed in vacuo, and ca. 100 mL of Et_2O was added. The mixture was extracted 5 times with 10% HCl. The aqueous layer was basified with sodium carbonate and 40% NaOH. The mixture was extracted five times with Et_2O. The Et_2O was removed in vacuo to give an oil. The oil was dissolved in 80 mL of 10% HCl and heated at reflux for 30 min. After cooling, the mixture was extracted five times with Et_2O. The organic layer was then extracted five times with 10% NaOH. The aqueous layer was acidified and extracted five times with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a solid. The solid was recrystallized from CH_2Cl_2 to give 4.11 g (75%) of 3-(*o*-bromophenyl)-*n*-propionic acid as a white crystalline solid: mp 99–100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 11.90 (br, 1 H, CO_2H), 7.50–7.53 (m, 1 H, Ar*H*), 7.20–7.35 (m, 2 H, Ar*H*), 7.02–7.17 (m, 1 H, Ar*H*), 3.07 (t, 2 H, $COCH_2$, J = 7.8 Hz), 2.71 (t, 2 H, Ar*H*, J = 8.0 Hz); IR (KBr, cm^{-1}) 2910 (w), 1705 (s), 1438 (s), 1273 (m), 1238 (s), 775 (s), 750 (s).

Anal. Calcd for $C_9H_9BrO_2$: C, 47.19; H, 3.96; Br, 34.88. Found: C, 47.06; H, 3.90; Br, 34.79.

To 4.07 g (0.019 mol) of 3-(*o*-bromophenyl)-*n*-propionic acid in 100 mL of THF at 0 °C was added 26 mL (0.026 mol) of borane–THF complex. After addition, the reaction mixture was warmed to room temperature for 20 min. At this time, the reaction was heated to reflux for 1 h. The solution was cooled to 0 °C and then quenched by the slow addition of 10 mL of H_2O. The solution was concentrated in vacuo, and to the mixture was added ca. 50 mL of Et_2O. The mixture was extracted twice with Na_2CO_3 (saturated), and the organic layer was dried over $MgSO_4$. The organic layer was concentrated in vacuo to give 3.798 g (99%) of 3-(*o*-bromophenyl)-1-propanol of sufficient purity to proceed to the next step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.55 (m, 1 H, Ar*H*), 7.16–7.28 (m, 2 H, Ar*H*), 6.95–7.10 (m, 1 H, Ar*H*), 3.66 (t, 2 H, CH_2O, J = 5.7 Hz), 2.82 (t, 2 H, ArCH_2, J = 5.9 Hz), 1.80–1.95 (m, 2 H, ArCCH_2); IR (neat, cm^{-1}) 3312 (s), 2940 (s), 1470 (s), 1437 (s), 1159 (m), 1018 (s), 748 (s).

To 3.80 g (17.6 mmol) of 3-(*o*-bromophenyl)-1-propanol in 110 mL of THF was added 2.97 (1.76 mmol) of *N*-hydroxyphthalimide and 4.68 g (17.6 mmol) of triphenylphosphine. The solution was then cooled to 0 °C, and 3.11 mL (19.4 mmol) of diethyl azodicarboxylate was added. The solution was then allowed to warm to room temperature overnight. The THF was removed in vacuo to give a crude solid. The solid was recrystallized from methanol to give a white crystalline solid. Three more crops were obtained and added to the first. To the solid was added 5 mL of EtOAc. The solution was separated from the solid by filtration through a pipet containing a cotton plug and directly onto the Chromatotron. The solid was washed four more times with 5-mL portions of EtOAc. Using 15% EtOAc, the material was purified to give 3.88 g (61%) of *N*-[[3-(*o*-bromophenyl)-*n*-propyl]oxy]phthalimide as a white crystalline solid: mp 91–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68–7.90 (m, 4 H, Ar*H*), 7.18–7.56 (m, 3 H, Ar*H*), 6.98–7.13 (m, 1 H, Ar*H*), 4.24 (t, 2 H, CH_2O, J = 6.2 Hz), 3.00 (t, 2 H, ArCH_2, J = 6.8 Hz), 2.00–2.18 (m, 2 H, ArCCH_2); IR (KBr, cm^{-1}) 2940 (w), 1780 (m), 1725 (s), 1465 (m), 1186 (s), 1018 (s), 990 (s), 878 (s).

Anal. Calcd for $C_{17}H_{14}BrNO_3$: C, 56.68; H, 3.92; N, 3.89; Br, 22.18. Found: C, 56.85; H, 3.86; N, 3.84; Br, 22.08.

To 5.04 g (14.0 mmol) of *N*-[[3-(*o*-bromophenyl)-*n*-propyl]oxy]phthalimide in 220 mL of ethanol was added 2.87 mL of 55% hydrazine hydrate. The solution was then heated at reflux for 3 h. After cooling, the ethanol was removed in vacuo to give a solid. To the solid was added 150 mL of 40% NaOH and 50 mL of Et_2O. The organic layer was separated, and the aqueous layer was washed four more times with ca. 50 mL of Et_2O. The organic layers were combined and dried over Na_2SO_4. The solvent was removed in vacuo to give 3.10 g (96%) of *O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine as a clear liquid, which was of sufficient purity to continue to the step: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.56 (m, 1 H, Ar*H*), 7.15–7.28 (m, 2 H, Ar*H*), 6.98–7.14 (m, 1 H, Ar*H*), 5.38 (br, 2 H, NH_2), 3.71 (t, 2 H, CH_2O, J = 6.4 Hz), 2.79 (t, 2 H, ArCH_2, J = 7.6 Hz), 1.82–2.01 (m, 2 H, ArCCH_2); IR (neat, cm^{-1}) 3312 (m), 2928 (s), 1586 (s), 1437 (s), 1123 (m), 1016 (s).

To 1.66 g (7.23 mmol) of *O*-[3-(o-bromophenyl)-*n*-propyl]-hydroxylamine in 7 mL of ethanol at 0 °C was added 0.56 mL (7.23 mmol) of 40% formaldehyde solution. After 20 min at this temperature, 2.4 mL of borane–pyridine complex was added. The solution was then warmed to room temperature. After 3 h at room temperature, the solution was cooled to 0 °C, and 24 mL of a 10% HCl solution was added dropwise. After addition, the solution was warmed to room temperature overnight. The ethanol was removed in vacuo, and ca. 30 mL of Et_2O was added. The mixture was basified using 40% NaOH and then extracted five times with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give an oil. The oil was separated using MPLC and 10% EtOAc/hexane to give 0.76 g (43%) of *N*-methyl-*O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine (11) as a clear colorless liquid: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.57 (m, 1 H, Ar*H*), 7.18–7.27 (m, 2 H, Ar*H*), 6.97–7.10 (m, 1 H, Ar*H*), 5.25–5.70 (br, 1 H, N*H*), 3.72 (t, 2 H, CH_2O, J = 6.8 Hz), 2.80 (t, 2 H, ArCH_2, J = 7.6 Hz), 2.73 (s, 3 H, NCH_3), 1.82–1.98 (m, 2 H, ArCH_2); IR (neat, cm^{-1}) 3267 (m), 2949 (s), 1566 (m), 1470 (s), 1055 (s), 1020 (s), 750 (s).

Anal. Calcd for $C_{10}H_{14}BrNO$: C, 49.20; H, 5.78; N, 5.74; Br, 32.73. Found: C, 49.27; H, 5.82; N, 5.70; Br, 32.71.

***N*-Methyl-*O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine-d_2,d_3 (11-d_2, 11-d_3).** To 4.51 mL (0.035) of 2,4,4-trimethyl-2-oxazoline in 100 mL of THF at −78 °C was added 26.5 mL (0.035 mol) of *n*-butyllithium. After 0.5 h at this temperature, 8.7 g (0.035 mol) of *o*-bromobenzyl bromide in 15 mL of THF was

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added. The solution was then warmed to room temperature. After 1 h at room temperature, the reaction was quenched with 5 mL of H_2O. The solvent was removed in vacuo, and ca. 100 mL of Et_2O was added. The mixture was extracted five times with 10% HCl. The aqueous layer was basified with sodium carbonate and 40% NaOH. The mixture was extracted five times with Et_2O. The Et_2O was removed in vacuo to give an oil. The oil was dissolved in 100 mL of 10% HCl and heated at reflux for 30 min. After cooling, the mixture was extracted five times with Et_2O. The organic layer was then extracted five times with 10% NaOH. The aqueous layer was acidified and extracted five times with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a solid. The solid was recrystallized from CH_2Cl_2 to give 5.82 g (72%) of 3-(*o*-bromophenyl)-*n*-propionic acid as a white crystalline solid whose spectral data matched that of previously synthesized material: mp 99–100 °C.

To 1.60 g (38.0 mmol) of lithium aluminum deuteride in 40 mL of Et_2O at 0 °C was added dropwise 5.82 g of 3-(*o*-bromophenyl)-*n*-propionic acid in 60 mL of THF. After addition, the reaction was heated at reflux for 1 h. The mixture was cooled to 0 °C, and 10 mL of EtOAc was added slowly. After reaction, the mixture was poured into ca. 100 g of crushed ice. To this mixture was added 80 mL of 20% HCl. The layers were separated, and the aqueous phase was washed three times with ethyl ether. The organic layers were combined and dried over $MgSO_4$ and concentrated in vacuo to give 5.45 g (94%) of 3-(*o*-bromophenyl)-1-propanol-d_2 as a clear colorless liquid of sufficient purity to proceed to the next step: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.45–7.55 (m, 1 H, Ar*H*), 7.16–7.28 (m, 2 H, Ar*H*), 6.95–7.10 (m, 1 H, Ar*H*), 2.82 (t, 2 H, ArCH_2, J = 7.9 Hz), 1.86 (t, 2 H, ArCCH_2, J = 7.8 Hz); IR (neat, cm^{-1}) 3387 (s), 2934 (s), 2203 (m), 2100 (m), 1470 (s), 1437 (s), 1136 (m), 1024 (s), 964 (s), 748 (s).

To 5.21 g (2.40 mmol) of 3-(*o*-bromophenyl)-1-propanol-d_2 in 150 mL of THF was added 3.91 (24.0 mmol) of *N*-hydroxyphthalimide and 6.29 g (24.0 mmol) of triphenylphosphine. The solution was then cooled to 0 °C, and 4.1 mL (26.0 mmol) of diethyl azodicarboxylate was added. The solution was then allowed to warm to room temperature overnight. The THF was removed in vacuo to give a crude solid. The solid was recrystallized from methanol to give 6.40 g (74%) of *N*-[[3-(*o*-bromophenyl)-*n*-propyl]oxy]phthalimide-d_2 as a white crystalline solid: mp 91–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.68–7.90 (m, 4 H, Ar*H*), 7.18–7.56 (m, 3 H, Ar*H*), 6.98–7.13 (m, 1 H, Ar*H*), 3.01 (t, 2 H, ArCH_2, J = 7.6 Hz), 2.09 (t, 2 H, ArCCH_2, J = 7.4 Hz); IR (KBr, cm^{-1}) 2920 (w), 2110 (m), 1770 (m), 1730 (s), 1465 (m), 1185 (s), 990 (s).

To 6.40 g (14.0 mmol) of *N*-[[3-(*o*-bromophenyl)-*n*-propyl]-oxy]phthalmide-d_2 in 250 mL of ethanol was added 3.6 mL of 55% hydrazine hydrate. The solution was then heated at reflux for 3 h. After cooling, the ethanol was removed in vacuo to give a solid. To the solid were added 150 mL of 40% NaOH and 50 mL of Et_2O. The organic layer was separated, and the aqueous layer was washed four more times with ca. 50 mL of Et_2O. The organic layers were combined and dried over Na_2SO_4. The solvent was removed in vacuo to give 4.06 g (99%) of *O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine-d_2 as a clear liquid, which was of sufficient purity to continue to the step: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.56 (m, 1 H, Ar*H*), 7.15–7.28 (m, 2 H, Ar*H*), 6.98–7.14 (m, 1 H, Ar*H*), 5.38 (br, 2 H, NH_2), 2.79 (t, 2 H, ArCH_2, J = 7.8 Hz), 1.88 (t, 2 H, ArCCH_2, J = 7.6 Hz); IR (neat, cm^{-1}) 3312 (m), 2936 (s), 2193 (m), 2093 (m), 1584 (s), 1470 (s), 1198 (m), 1020 (s), 748 (s).

To 2.02 g (8.70 mmol) of *O*-[3-(*o*-bromophenyl)-*n*-propyl]-hydroxylamine-d_2 in 10 mL of ethanol at 0 °C was added 0.65 mL (8.70 mmol) of 37% formaldehyde solution. After 20 min at this temperature, approximately 3 equiv of borane-d_3–pyridine complex was added. The solution was then warmed to room temperature. After 1.5 h at room temperature, the solution was cooled to 0 °C, and 30 mL of a 10% HCl solution was added dropwise. After addition, the solution was warmed to room temperature overnight. The ethanol was removed in vacuo, and ca. 30 mL of Et_2O was added. The mixture was basified using 40% NaOH and then extracted five times with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give an oil. The oil was separated using MPLC and 10% EtOAc/hexane to give 0.59 g (27%) of *N*-methyl-*O*-[3-(*o*-bromophenyl)-*n*-propyl]hydroxylamine-d_2,d_3 as a clear colorless liquid and 1.03 g of starting material. The deuterium incorporation was by GC–MS and examination of the m/e M$^+$ – Br signal: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.48–7.57 (m, 1 H, Ar*H*), 7.18–7.27 (m, 2 H, Ar*H*), 6.97–7.10 (m, 1 H, Ar*H*), 5.25–5.70 (br, 1 H, N*H*), 2.79 (t, 2 H, ArCH_2, J = 7.6 Hz), 2.66–2.74 (m, 2 H, NCH_2D), 1.88 (t, 2 H, ArCCH_2, J = 7.8 Hz); IR (neat, cm^{-1}) 3275 (m), 2934 (s), 2189 (m), 2091 (m), 1566 (m), 1469 (s), 1437 (s), 1055 (s), 1022 (s), 748 (s); GC–MS (200 °C) t_R 2.52 min, m/e (relative intensity) 164 (0.4), 165 (0.5), 166 (314238), 167 (100); 25% d_2 75% d_3.

General Procedure for the Reaction of Organolithium Reagents with Methoxylamine/Methyllithium. To a flask containing 2 equiv of methyllithium at –78 °C was added dropwise using a double-tipped needle a precooled solution of 2 equiv of methoxylamine in hexane. To this was immediately added 1 equiv of the organolithium reagent to be aminated. The mixture was then warmed to –15 °C for 2 h. The mixture was then quenched with water, and either the benzamide or the acetamide was formed by reaction with benzoyl chloride or acetyl chloride in the presence of pyridine. Et_2O was then added, and the mixture was extracted three times each with 10% HCl, 10% NaOH, and brine. The organic phase was dried over $MgSO_4$, and the solvent was evaporated in vacuo. The remaining oil was then purified by MPLC, or if a solid was obtained, it was recrystallized.

Amination of *p*-Lithiotoluene with Methoxylamine/Methyllithium. The reaction was carried out with 3.0 mL (2 mmol) of methyllithium in Et_2O, 0.094 g (2 mmol) of methoxylamine in 2 mL of hexane, 4.2 mL (1 mmol) of *p*-lithiotoluene in Et_2O, 0.06 mL of water, 1 mL of benzoyl chloride, and 2 mL of pyridine. Upon evaporation of the solvent, a crude solid was obtained. Recrystallization from EtOAc/hexane gave 0.196 g (93%) of *N*-*p*-tolylbenzamide as a white solid: mp 157–158 °C (lit.[18] mp 158 °C); ^{1}H NMR (200 MHz, DMSO-d_6) δ 10.15 (br, 1 H, N*H*), 7.92–7.97 (m, 2 H, Ar*H*), 7.47–7.68 (m, 5 H, ar*H*), 7.15 (m, 2 H, ar*H*), 2.28 (s, 3 H, ArCH_3); IR (KBr, cm^{-1}) 3400 (m), 3315 (m), 1648 (s), 1530 (m), 1500 (m), 1318 (m), 813 (m).

Amination of Diphenylcuprate with Methoxylamine/Methyllithium. To 3.8 mL (4 mmol) of methyllithium in Et_2O at –78 °C was added dropwise a precooled solution of 0.188 g (4 mmol) of methoxylamine in 4 mL of hexane. To this was immediately added 1 mmol of diphenyl cuprate, prepared from the reaction of 2.9 mL (2 mmol) of phenyllithium with 0.208 g (1 mmol) of copper bromide dimethyl sulfide in Et_2O for 20 min at –78 °C. The mixture was then taken to –15 °C for 2 h and quenched with 2 mL of benzoyl chloride. To this was then added 30 mL of NH_4Cl/NH_4OH (pH = 8), and the mixture was allowed to stir overnight. The mixture was then diluted with Et_2O and extracted three times each with 10% NaOH and brine. Concentration in vacuo gave a crude solid. Recrystallization from benzene gave 0.330 g (83%) of *N*-phenylbenzamide as a white solid whose spectral data matched that of previously synthesized material: mp 164–165 °C (lit.[18] mp 163 °C).

Amination of *n*-Butyllithium with *N*-*n*-Propylmethoxylamine. To 2.0 mL (2.53 mmol) of methyllithium in Et_2O at –78 °C was slowly added 0.225 g (2.53 mmol) of *N*-*n*-propylmethoxylamine in 2 mL of hexane. To this solution was then added 1.8 mL (2.53 mmol) of *n*-butyllithium in hexane all at once. The solution was then warmed to –15 °C, where it was allowed to remain for 3 h. At this time, the reaction was quenched with 1.06 g (7.60 mmol) of benzoyl chloride. The mixture was then allowed to warm to room temperature overnight. Approximately 20 mL of Et_2O was added, and the mixture was extracted three times each with 10% HCl, 10% NaOH, and brine. The organic layer was dried over $MgSO_4$, concentrated in vacuo, and submitted to MPLC separation using 2% EtOAc/hexane. There was obtained 0.361 g (65%) of *N*-*n*-propyl-*N*-*n*-butylbenzamide as a clear colorless liquid, whose spectral data matched that of authentic material (vide infra): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28–7.35 (m, 5 H, Ar*H*), 3.35–3.55 (m, 2 H, NCH_2), 3.02–3.30 (m, 2 H, NCH_2), 1.30–1.80 (m, 6 H, NCCH_2CH_2, NCCH_2), 0.70–1.20 (m, 6 H, CCH_3, CCH_3); IR (neat, cm^{-1}) 2959 (s), 2933 (s), 2873 (s), 1636 (s), 1464 (m), 1444 (m), 1423 (s), 1100 (m), 788 (m), 700 (s); MS (10 eV) m/e (relative intensity) 219 (7), 218 (3), 190 (3), 176 (5), 106 (7),

(18) *Handbooks of Tables for Organic Compound Identification*; Rappaport, Z., Ed.; CRC Press, Inc.: Boca Raton, FL, 1980.

105 (100), 77 (16), 50 (6), 39 (3).

Amination of *n*-Butyllithium with *N*-Isopropylmethoxylamine. To 0.95 mL (1.66 mmol) of methyllithium at −78 °C was slowly added a precooled solution of 0.147 g (1.66 mmol) of *N*-isopropylmethoxylamine in 0.75 mL of hexane. After 5 min at −78 °C, 1.23 mL (1.66 mmol) of *n*-butyllithium in hexane was added. The solution was warmed to −15 °C, where it stirred for 1 h. At this time, the solution was allowed to warm to room temperature overnight. The solution was then cooled to 0 °C, and 0.81 mL (7.0 mmol) of benzoyl chloride was added. The mixture was allowed to stir overnight. To the mixture was added 50 mL of Et_2O, and the mixture was extracted three times each with 10% NaOH and 10% HCl and once with brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give an oil. The oil was purified by MPLC using 10% EtOAc/hexane to give an oil, which was distilled using a Kugelrohr apparatus to give 0.17 g (47%) of *N*-*n*-butyl-*N*-isopropylbenzamide as a clear colorless oil: bp 100 °C (1 mmHg); ^1H NMR (200 MHz, $CDCl_3$, 20 °C) δ 7.28–7.43 (m, 5 H, Ar*H*), 3.69–4.13 (br, 1 H, NC*H*), 2.98–3.32 (br, 2 H, NCH_2), 0.55–2.15 (br, 13 H, $NC(CH_3)_2$, $NCCH_2CH_2CH_3$); ^1H NMR (200 MHz, toluene-d_8, 60 °C) d 7.05–7.29 (m, 4 H, Ar*H*), 4.03 (sep, 1 H, NC*H*, J = 6.9 Hz), 3.08–3.18 (m, 2 H, NCH_2), 1.47–1.63 (m, 2 H, $NCCH_2$), 1.08–1.28 (m, 2 H, $NCCCH_2$), 0.93 (d, 6 H, $NC(CH_3)_2$, J = 6.8 Hz), 0.75–0.88 (m, 3 H, $NCCCCH_3$); IR (neat, cm^{-1}) 2961 (s), 2874 (s), 1632 (s), 1445 (s), 1418 (s), 1345 (s), 1198 (m), 1103 (s), 1028 (s), 783 (m).

Anal. Calcd for $C_{14}H_{21}NO$: C, 76.67; H, 9.65; N, 6.39. Found: C, 76.53; H, 9.67; N, 6.38.

Amination of *sec*-Butyllithium with *N*-Benzylmethoxylamine. To 3.4 mL (3.3 mmol) of methyllithium in Et_2O at −78 °C was added dropwise a precooled solution of 0.450 g (3.3 mmol) of *N*-benzylmethoxylamine in 4 mL of hexane. After 20 min at this temperature, 1.43 mL (1.65 mmol) of *sec*-butyllithium in cyclohexane was added all at once. The mixture was warmed to −15 °C for 2 h. The reaction was then quenched with methanol and extracted three times with brine. The organic layer was separated by MPLC using 40% EtOAc/hexane to give 0.089 g (16%) of *N*-*sec*-butyl-*N*-benzylamine as an oil, whose analytical data matched that of authentic material (vide infra): ^1H NMR (200 MHz, $CDCl_3$) δ 7.20–7.40 (s, 5 H, Ar*H*), 3.75 (dd, 2 H, $ArCH_2$), 2.53–2.70 (m, 1 H, NC*H*), 1.26–1.70 (m, 2 H, $NCCH_2$), 1.20 (br, 1 H, N*H*) 1.07 (d, 3 H, $NCCH_3$, J = 6.6 Hz), 0.89 (t, 3 H, $NCCCH_3$, J = 7.2 Hz); IR (neat, cm^{-1}) 3312 (w), 3086 (m), 3063 (m), 2961 (s), 2926 (s), 2872 (s), 1603 (w), 1495 (m), 1452 (s), 1373 (s), 1344 (m), 1165 (m), 1071 (m), 1028 (m), 966 (w).

Amination of *n*-Butyllithium with *N*-(1-Phenylethyl)methoxylamine at −15 °C. The method was used in which *N*-(1-phenylethyl)methoxylamine was treated first with methyllithium followed by treatment with *n*-butyllithium.[2] The mixture was warmed to −15 °C for 3 h and the product, *N*-*n*-butyl-*N*-(1-phenylethyl)amine, was isolated as the free base, 0.154 g (43%). The spectral properties of *N*-*n*-butyl-*N*-(1-phenylethyl)amine matched those of authentic material.

Intramolecular Amination of *N*-(*o*-Bromobenzyl)methoxylamine To Give 1. To 1 mL (1.3 mmol) of methyllithium in Et_2O at −78 °C was added dropwise a precooled solution of 0.291 g (1.3 mmol) of *N*-(*o*-bromobenzyl)methoxylamine in 5 mL of hexane. To this was immediately added 0.85 mL (1.3 mmol) of *n*-butyllithium. The mixture was then allowed to stir for 30 min at −78 °C. The reaction was then warmed to −15 °C for 3 h. The reaction was quenched with 0.05 mL of water followed by the addition of 2.3 mL of acetyl chloride and 2.6 mL of pyridine. Et_2O was added, and the mixture was extracted three times each with 10% HCl, 10% NaOH, and brine. The organic phase was dried over $MgSO_4$ and then concentrated in vacuo. The crude oil was separated by MPLC using 25% EtOAc/hexane. This provided 0.040 g (21%) of *N*-acetylbenzoazetine (1) as a white solid: mp 89–90 °C; ^1H NMR (200 MHz, toluene-d_8, 20 °C) δ 7.10–7.40 (m, 4 H, Ar*H*), 4.58–4.15 (s, 2 H, CH_2), 1.9–1.63 (s, 3 H, $COCH_3$); ^1H NMR (200 MHz, toluene-d_8, 100 °C) δ 7.10–7.40 (m, 4 H, Ar*H*), 4.55 (s, 2 H, CH_2), 1.92 (s, 3 H, $COCH_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 129.6, 128.3, 123.5, 123.3, 122.2, 121.4, 111.1, 108.7, 60.3, 57.9, 30.2, 22.2; IR (KBr, cm^{-1}) 1652 (s), 1600 (m), 1471 (s), 1463 (s), 1328 (m), 1129 (w), 752 (s); MS (10 eV) *m/e* (relative intensity) 147 (100, M^+), 146 (17), 106 (10), 105 (43), 104 (45), 78 (22), 58 (25), 43 (44); MS (field ionization, 30 °C) *m/e* 147. Vapor-phase osmometry (benzene, 45 °C) 165 ± 15; MS (high resolution) *m/e* calcd for C_9H_9NO 147.068, found 147.068.

Anal. Calcd for C_9H_9NO: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.80; H, 6.36; N, 9.43.

Intramolecular Amination of *N*-[3-(*o*-Bromophenyl)propyl]methoxylamine To Give 2. To 3.4 mL (1.27 mmol) of methyllithium at −78 °C was added 0.311 g (1.27 mmol) of *N*-[3-(*o*-bromophenyl)propyl]methoxylamine in 1 mL of hexane and 2 mL of THF. After addition, 1.45 mL (2.45 mmol) of *tert*-butyllithium was added, and the reaction was allowed to stir for an additional 30 min at −78 °C. At this time the temperature was raised to −15 °C where it remained for 3 h. The reaction was then quenched with 0.36 mL (5.0 mmol) of acetyl chloride, and the reaction was allowed to warm to room temperature overnight. The solvent was removed in vacuo, and ethyl ether was added. The reaction mixture was extracted three times with 10% HCl and 10% NaOH and once with brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to give an oil. The oil was separated by MPLC using 10% EtOAc/hexane and distilled using a Kugelrohr apparatus to give 0.142 g (64%) of *N*-acetyl-1,2,3,4-tetrahydroquinoline (2) as a clear colorless oil: bp 105 °C (1 mmHg); ^1H NMR (200 MHz, $CDCl_3$) δ 7.05–7.30 (m, 4 H, Ar*H*), 3.79 (t, 2 H, NCH_2, J = 6.2 Hz), 2.72 (t, 2 H, $ArCH_2$, J = 6.4 Hz), 2.23 (s, 3 H, $COCH_3$), 1.92–2.02 (m, 2 H, $ArCCH_2$); IR (neat, cm^{-1}) 2942 (m), 1649 (s), 1603 (m), 1579 (m), 1491 (s), 1379 (s), 1334 (s), 760 (s). To further identify this material, the *N*-benzoyl-1,2,3,4-tetrahydroquinoline derivative was prepared. To 0.100 g of the oil was added 10 mL of concentrated HCl. The mixture was then heated to 105 °C for 14 h when it was cooled. The solution was basified with 40% NaOH and extracted five times with Et_2O. The organic layer was dried over Na_2SO_4 and concentrated in vacuo to give 0.064 g (85%) of 1,2,3,4-tetrahydroquinoline as a light yellow oil. The oil was dissolved in 10 mL of Et_2O and cooled to 0 °C, and 1 mL of NEt_3 and 0.07 mL of benzoyl chloride were added consecutively. The mixture was allowed to warm to room temperature over 12 h. The mixture was extracted three times each with 10% NaOH and 10% HCl and once with brine. The organic layer was dried over $MgSO_4$ and concentrated in vacuo to give a solid. The solid was recrystallized from EtOAc/hexane to give 0.097 g (60%) of *N*-benzoyl-1,2,3,4-tetrahydroquinoline as a white solid: mp 74–76 °C (lit.[14] mp 75 °C).

Intramolecular Amination of *N*-[4-(*o*-Bromophenyl)-*n*-butyl]methoxylamine To Give 3. To 0.75 mL (1.32 mmol) of methyllithium at −78 °C was added 0.340 g (1.32 mmol) of *N*-[4-(*o*-bromophenyl)-*n*-butyl]methoxylamine in 4 mL of hexane and 1 mL of THF. After addition, 1.67 mL (2.64 mmol) of *tert*-butyllithium was added, and the reaction was allowed to stir an additional 30 min at −78 °C. At this time the temperature was raised to −15 °C, where it remained for 3 h. The reaction was then quenched with 5 equiv of acetyl chloride, and the reaction mixture was allowed to warm to room temperature over 18 h. The solvent was removed in vacuo, and Et_2O was added. The reaction mixture was extracted twice each with 10% HCl and 10% NaOH and once with brine. The organic layer was dried over $MgSO_4$, and the solvent was removed in vacuo to give an oil. The oil was separated using MPLC and 25% EtOAc/hexane to give 0.060 g (24%) of *N*-acetyl-1-benzazepine (3) as a clear colorless oil whose spectral data matched that of authentic material: ^1H NMR (200 MHz, $CDCl_3$) δ 7.08–7.30 (m, 4 H, Ar*H*), 4.63–4.77 (m, 2 H, NCH_2), 2.52–2.88 (m, 4 H, $ArCH_2$, $NCCH_2$), 169–2.08 (m, 2 H, $ArCCH_2$), 1.86 (s, 3 H, $COCH_3$); IR (neat, cm^{-1}) 2930 (m), 2843 (m), 1648 (s), 1598 (m), 1495 (s), 1396 (s), 1312 (s), 1036 (m), 954 (m), 777 (s).

Amination with *N*-Methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine. To 2.02 mL (1.7 mmol) of methyllithium at −78 °C was added dropwise a precooled solution of 0.41 g (1.7 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine in 8 mL of hexane. After addition, 2.5 mL (3.4 mmol) of *tert*-butyllithium was added. The solution was then stirred for 30 min at −78 °C. The solution was warmed to −15 °C, where it was allowed to stir for 3 h. The reaction was then quenched with water and cooled to −78 °C. To the solution was added 1.25 mL of acetyl chloride, and the reaction was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with

brine. After drying over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was purified using MPLC and 50% EtOAc to give 0.22 g (ca. 70%) of a mixture of 3-phenyl-*n*-propyl acetate and 3-(*o*-bromophenyl)-*n*-propyl acetate and 0.05 g (12%) of *N*-methyl-*o*-(3-acetoxypropyl)acetanilide (**12**) as a clear liquid: ^1H NMR (200 MHz, $CDCl_3$) δ 7.09-7.38 (m, 4 H, Ar*H*), 4.11 (t, 2 H, CH_2O, J = 6.3 Hz), 3.20 (s, 3 H, NCH_3), 2.64 (t, 2 H, $ArCH_2$, J = 7.3 Hz) 2.06 (s, 3 H, $COCH_3$), 1.86-2.05 (m, 2 H, $ArCCH_2$), 1.77 (s, 3 H, $COCH_3$); IR (neat, cm^{-1}) 2959 (m), 1738 (s), 1662 (s), 1601 (m), 1493 (s), 1453 (s), 1379 (s), 1034 (s), 775 (m); GLPC-MS (190 °C) t_R 2.88 min; m/e (relative height) 249 (M^+, 39), 192 (32), 174 (32), 148 (95), 146 (100), 91 (50).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.41; H, 7.70; N, 5.62. Found: C, 67.23; H, 7.62; N, 5.59.

Double-Labeling Crossover Experiments with 24, 24-d_2,d_3. Run 1. To 1.90 mL (2.06 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.2441 g (0.988 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.2615 g (1.070 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 10 mL of hexane. After addition, 3.6 mL (4.12 mmol) of *tert*-butyllithium was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 3 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After being dried over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min; m/e (relative height) 252 (67), 251 (100), 250 (74), 249 (85), 248 (50); calcd % d = 33% d_0, 19% d_1, 31% d_2, 17% d_3.

Run 2. To 0.68 mL (0.74 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.1061 g (0.435 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.0745 g (0.302 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 3 mL of hexane. After addition, 1.29 mL (1.48 mmol) of *tert*-butyllithium was added. After this addition 8 mL of cooled hexane was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 3 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After drying over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min; m/e (relative height) 252 (43), 251 (82), 250 (56), 249 (100), 248 (0.4); calcd % d = 42% d_0, 16% d_1, 31% d_2, 12% d_3.

Run 3. To 0.99 mL (1.07 mmol) of methyllithium at -78 °C was added dropwise a precooled solution of 0.1555 g (0.637 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine and 0.1087 g (0.440 mmol) of *N*-methyl[[3-(*o*-bromophenyl)-*n*-propyl]oxy]methoxylamine-d_2,d_3 in 6 mL of hexane. After addition, 1.9 mL (2.14 mmol) of *tert*-butyllithium was added. The solution was then stirred for 30 min at -78 °C. The solution was warmed to -15 °C, where it was allowed to stir for 1.5 h. The reaction was then quenched with water and cooled to -78 °C. To the solution was added 1.50 mL of acetyl chloride, and the reaction mixture was allowed to warm to room temperature. After 48 h, the mixture was extracted twice with 10% HCl and 10% NaOH and once with brine. After being dried over $MgSO_4$, the solution was concentrated in vacuo to give an oil. The oil was then analyzed using capillary GLPC-MS: GLPC-MS (190 °C) t_R 2.87 min, m/e (relative height) 252 (42), 251 (77), 250 (54), 249 (100), 248 (71); calcd % d = 43% d_0, 16% d_1, 29% d_2, 12% d_3.

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Supplementary Material Available: The preparations of methoxylamine, *N*-*n*-propylmethoxylamine, *N*-isopropylmethoxylamine, *N*-benzylmethoxylamine, *N*-[3-(*o*-bromophenyl)-*n*-propyl]methoxylamine (**11**), *N*-[4-(*o*-bromophenyl)-*n*-butyl]-methoxylamine, *N*-*n*-propyl-*O*-methyl-*p*-nitrobenzohydroxamic acid, *N*-isopropyl-*O*-methyl-*p*-nitrobenzohydroxamic acid, *N*-acetylbenzazepine (**3**), *N*-*n*-propyl-*N*-*n*-butylbenzamide, *N*-*sec*-butyl-*N*-benzylamine, the aryllithium reagents, the aminations in Schemes I-III, and the X-ray crystallographic data for *N*-acetylbenzoazetine (**1**) (30 pages). Ordering information is given on any current masthead page.

An Approach to Amphimedine and Related Marine Alkaloids Utilizing an Intramolecular Kondrat'eva Pyridine Synthesis[1]

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A strategy for the synthesis of the marine alkaloid amphimedine (**1**) and its congeners **2-5** has been investigated. The approach involves an intramolecular Diels-Alder reaction of a 4,5-disubstituted oxazole (Kondrat'eva reaction) to produce the ABC ring system of these natural products, followed by a photoenolization/electrocyclization to construct the D ring. The key oxazole olefin **30** was prepared in several steps starting from pyridine ester **10** and *o*-aminostyrene (**19**). The route to **30** utilized a Kozikowski modification of the Schollkopf oxazole synthesis as a key step. Thermolysis of oxazole **30** provided fused pyridine **31** via the desired [4 + 2] cycloaddition. Attempts to cyclize derived aldehyde **32** photochemically failed, affording primarily decarbonylation products.

Marine organisms have been the source of a wide variety of novel natural products. Although many terpenoids and related molecules are known, very few alkaloids have been isolated from marine sources. Amphimedine (**1**), a structurally unique pentacyclic aromatic alkaloid, was isolated in 1983 by Schmitz and co-workers from an *Amphimedon* species of sponge collected near Guam Island.[2] More recently, the closely related alkaloids cystodytin A (**2**), B

(1) Taken in part from the Ph.D. Thesis of C. Subramanyam, The Pennsylvania State University, 1987.

(2) Schmitz, F. J.; Agarwal, S. K.; Gunasekara, S. P.; Schmidt, P. G.; Shoolery, J. N. *J. Am. Chem. Soc.* **1983**, *105*, 4835.

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