# Development of a Universal Alkoxyamine for "Living" Free Radical Polymerizations

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**Abstract:** Examination of novel alkoxyamines has demonstrated the pivotal role that the nitroxide plays in mediating the "living" or controlled polymerization of a wide range of vinyl monomers. Surveying a variety of different alkoxyamine structures led to α-hydrido derivatives based on a 2,2,5-trimethyl-4-phenyl-3-azahexane-3-oxy, **1**, skeleton which were able to control the polymerization of styrene, acrylate, acrylamide, and acrylonitrile based monomers. For each monomer set, the molecular weight could be controlled from 1000 to 200 000 amu with polydispersities typically 1.05−1.15. Block and random copolymers based on combinations of the above monomers could also be prepared with similar control. In comparison with 2,2,6,6-tetramethylpiperidinoxy (TEMPO), these new systems represent a dramatic increase in the range of monomers that can be polymerized under controlled conditions and overcome many of the limitations associated with nitroxide-mediated "living" free radical procedures. Monomer selection and functional group compatibility now approach those of ATRP-based systems.

## Introduction

The desire to prepare advanced materials with new and/or improved properties is a continuing focus in many academic and industrial laboratories. The driving force is the belief that these materials will offer substantial benefits in areas ranging from microelectronic fabrication, to catalyst design, to biotechnology. In the macromolecular arena, a common feature of many of these new materials is their well-defined nature with the number of functional groups, molecular weight, polydispersity, and the presence or absence of branching being precisely controlled.[1] Traditionally, such well-defined macromolecules were only available from living procedures,[2] such as anionic polymerization, which are synthetically challenging and not amenable to significant changes in the structure of the macromolecule, or the presence of functional groups. For example, simple random copolymers of styrene and methyl methacrylate cannot be prepared by living anionic procedures. Conversely, these random copolymers are trivially prepared using traditional free radical chemistry; however, the level of control is severely compromised leading to ill-defined, polydisperse materials. The desire to develop a simple and versatile method for the preparation of wide variety of well-defined polymeric materials has continued unabated, resulting in the recent development of "living" free radical polymerization techniques.

The field of living free radical polymerization[3] has expanded rapidly in recent years with major advances occurring in both nitroxide-mediated processes[4] and atom transfer radical procedures (ATRP).[5] In both strategies, the synthesis of functionalized unimolecular initiators[6] permits the preparation of a wide range of different materials which are either difficult to prepare or not available via other polymerization processes. For example, the architecture or topology of the polymer (i.e., comb, star, dendritic, etc.),[7] composition of the backbone (i.e., random, gradient, or block copolymer),[8] inclusion of functionality (i.e., chain-end, site-specific, etc.)[9] can all be readily manipulated using living free radical methodologies while still retaining a high degree of control over the molecular weight and polydis-

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persity. Similar capabilities have also been reported for the recently introduced radical addition and fragmentation technique (RAFT).[10]

In many respects, all of the living free radical techniques (nitroxide, ATRP, RAFT) are similar in their overall scope, although there are a number of subtle differences which affect the applicability and suitability of each system for specific applications. For example, nitroxide-mediated processes are potentially simpler since they do not require an added metal complex and this absence leads to a greater functional group tolerance and easier purification (no metal ion contamination). However, the major limitation of nitroxide-mediated procedures is their incompatibility with most vinyl monomer families. Typically, these are limited to styrene-based systems, and the level of control afforded to homopolymerization of acrylate/ methacrylates and even random copolymers with high acrylates/ methacrylate levels has been poor.[11] In contrast, ATRP techniques have been successfully applied to a wide range of monomer families, including styrenics, acrylates, methacrylates, and acrylonitrile. To greatly extend the field of living free radical polymerization, the development of a nitroxide-based system for the controlled polymerization of nonstyrenic monomers is therefore highly desirable.

Initial efforts to develop such a system has relied on the use of nitroxides other than 2,2,6,6-tetramethylpiperidinoxy (TEMPO) as the mediating radical. The Xerox group has polymerized acrylates at 145−155 °C in the presence of 4-oxo-TEMPO, **2**, as the mediating nitroxide, and while this is a significant improvement when compared to TEMPO, polydispersities were still between 1.40 and 1.67.[12] More recently, the same group has introduced the use of reducing additives such as hydroxy-acetone as a method for controlling the concentration of free nitroxide in these systems.[13] A significant increase in the rate of polymerization is observed; however, polydispersities are still between 1.40 and 1.95. The most successful approach to

**Scheme 1**
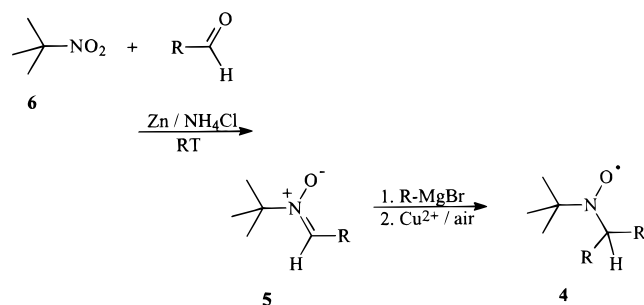


overcoming this limitation is the introduction of the phosphonate derivative, **3**, by Gnanou and Tordo[14] for the controlled polymerization of acrylates. In this seminal report, an initiating system consisting of a 2.5:1 mixture of **3** and AIBN gave poly-(acrylates) with polydispersities as low as 1.11. Interestingly, the structure of **3** is significantly different from that of other nitroxides that have been examined. This suggests that the *nitroxide structure* plays a crucial role in the success or failure of living free radical polymerizations, and the key to extending the scope of this reaction is in designing more effective nitroxides. On the basis of these pioneering results, we have explored a range of different nitroxides and their associated alkoxyamines in an effort to develop a universal system suitable for the polymerization of a significantly wider selection of monomers than is currently available. Such a system would be analogous to the sulfonyl halides that have been introduced by Percec as universal initiators for ATRP.[15]
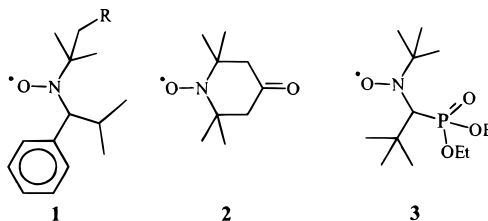


## Results and Discussion

A range of structurally diverse alkoxyamines were employed in this study. These were prepared from the corresponding nitroxides, many of which were available from the earlier work of Braslau et al.[16] in examining the stereoselective coupling of chiral nitroxides with prochiral carbon radicals.

A synthetic strategy was developed for the synthesis of a series of acyclic α-hydrogen bearing nitroxides, **4**, which were prepared from the corresponding tertiary nitro compounds and aldehydes according to Scheme 1. On the basis of the earlier work of Gnanou and Tordo, these were considered prime candidates due to their lower stability compared to traditional nitroxides such as TEMPO. Reductive condensation of 2-meth-yl-2-nitropropane, **6**, with a range of aldehydes gave the desired nitrones, **5**, in a single high-yielding step, which obviates the

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(15) Percec, V.; Barboui, B.; Kim, H. J. *J. Am. Chem. Soc.* **1998**, *120*, 305.

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**Scheme 2**
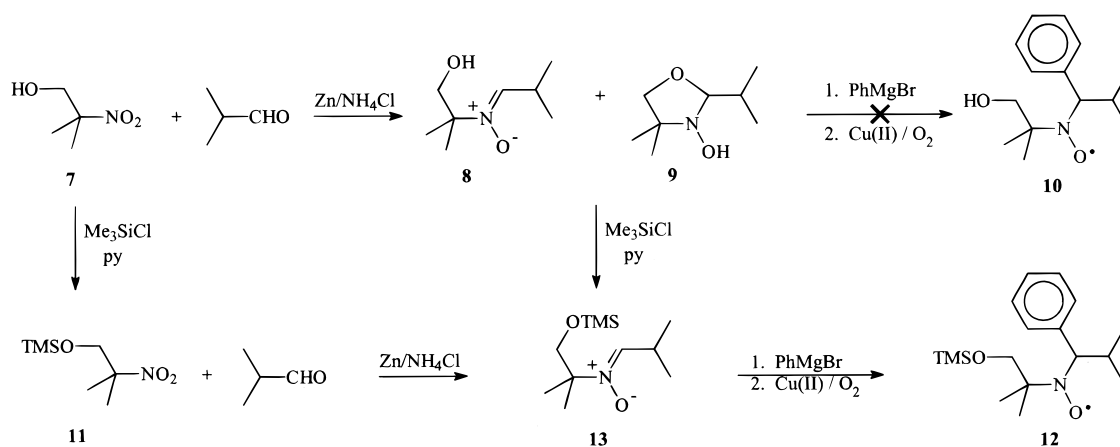


need to isolate the easily oxidizable alkyl hydroxylamine intermediates. Addition of a variety of aryl Grignards according to the method of Reznikov and Volodarsky,[17] followed by copper(II) catalyzed oxidation under ambient atmosphere resulted in the formation of the desired nitroxides **4**.

While 2-methyl-2-nitropropane, **6**, was primarily used as a starting material, the greater availability of 2-methyl-2-nitropropan-1-ol, **7**,[18] coupled with the presence of a functionalizable primary alcohol, suggested that **7** could also be a useful starting material. Application of the above procedure to **7** was complicated by the cyclization of the intermediate β-hydroxynitrone, **8**, to give an 3:2 equilibrium mixture of **8** and the hydroxylamine, **9**. Deprotonation of this mixture with phenylmagnesium bromide followed by addition of a second equivalent of Grignard reagent to the nitrone did not lead to the desired nitroxide, **10**. Instead, degradation was observed, presumably due to elimination of formaldehyde from the β-hydroxy hydroxyamine. This instability necessitated the protection of the hydroxy functionality; either the nitro derivative, **7**, could be protected as a trimethylsilyl ether, **11**, which could then be carried through the synthesis in high yields to give the protected nitroxide, **12**, or the equilibrium mixture of **8** and **9** could be treated with trimethylsilyl chloride and pyridine (Scheme 2). Although literature precedent[19] suggests that acylation of *N*-2-hydroxy-alkylnitrones gives the cyclic product, it was found that silylation gave only the desired open chain form, **13**, which could then be arylated with phenylmagnesium bromide, followed by oxidation to give the nitroxide, **12.**

One advantage of this strategy is that, after deprotection of the silyl group, the resulting nitroxide, or alkoxyamine, has a reactive hydroxy functionality which can be used to prepare telechelic polymers and chromophore-labeled materials for further study.[20] While the presence of the α-hydrogen decreases the stability of the nitroxide when compared to TEMPO, all of the above compounds were stable to storage at room temperature and could be purified by normal procedures, such as flash chromatography.

In an effort to further decrease the stability of the nitroxide, the α-tertiary carbon atom in **6** was replaced by a secondary carbon atom. The presence of an additional α-hydrogen atom

should substantially decrease the stability of the corresponding nitroxide, **14**. By using the same procedure as above, 2-nitropropane, **15**, was condensed with either isobutyryl aldehyde or trimethylacetaldehyde to give the nitrone derivatives, **16**−**17**, in good yield. Unfortunately, the treatment of **16**−**17** with phenylmagnesium bromide followed by copper-catalyzed oxidation did not yield isolatable amounts of the nitroxides, **14a**−**b**. In the case of the isopropyl nitrone, **16**, no product was observed, while for the sterically more demanding *tert*-butyl nitrone, **17**, the corresponding nitroxide could be observed by TLC but was not sufficiently stable to be isolated by chromatography or stored. To overcome the instability of these nitroxides, the intermediate hydroxyamines, **18**, were not oxidized with copper and air but were instead used directly in the formation of the alkoxyamines. In this way the hydroxyamines are oxidized in situ by PbO$_2$ to give the unstable nitroxides which can be trapped to give the alkoxyamines, **41**−**42**. This strategy proved successful and the desired alkoxyamines could be prepared, purified and stored under normal conditions (Scheme 3).

In the above strategies, a variety of aryl Grignard reagents can be used in the addition step; however, the yield of nitroxide obtained for sterically demanding Grignards, such as 2,4,6-trimethylphenylmagnesium bromide, was significantly decreased (ca. 25%), presumable due to steric congestion. Interestingly, attempts to extend this protocol to the Grignard reagent derived from bromopentafluorobenzene (Scheme 4) did not result in the perfluoroaryl nitroxide, **19**, but rather in the fused ring compound **20**, which presumably derives from a [2 + 3] dipolar addition to a benzyne intermediate.

An improved procedure for the phosphonate nitroxide **2**, first described by Tordo et al.,[21] was also developed due to difficulties experienced in following the reported procedures. Addition of diethyl phosphite to the imine, **21** (prepared by condensation of pivalaldehyde with *N-tert*-butylamine) gave the amino derivative, **22**, which was oxidized with *m*CPBA to give the nitroxide, **3**, in 24% overall yield (Scheme 5).

Synthesis of the alkoxyamine initiators from these nitroxides was then accomplished by two different methodologies. The nitroxide, **23**, could be coupled with the 1-phenethyl radical generated from PbO$_2$ oxidation of 1-phenethyl hydrazine as detailed recently by Braslau.[22] Alternatively, the nitroxide, **23**, could be added to styrene in the presence of Jacobsen's reagent

(17) Reznikov, V. A.; Gutorov, I. A.; Gatlov, Y. V.; Rybalova, T. V.; Volodarsky, L. B. *Russ. Chem. Bull*. **1996**, *45*, 384.

(18) 2-Methyl-2-nitropropan-1-ol, **7**, is substantially cheaper ($88 per kg) than 2-methyl-2-nitropropane, **6**, ($3000 per kg).

(19) Kliegel, W.; Enders, B.; Becker, H. *Chem. Ber*. **1983**, *116*, 27.

(20) Frank, B.; Gast, A. P.; Russell, T. P.; Brown, H. R.; Hawker, C. J. *Macromolecules* **1996**, *29*, 6531; Hedrick, J. L.; Hawker, C. J.; Dipietro, R.; Jerome, R.; Charlier, Y. *Polymer* **1995**, *36*, 4855.
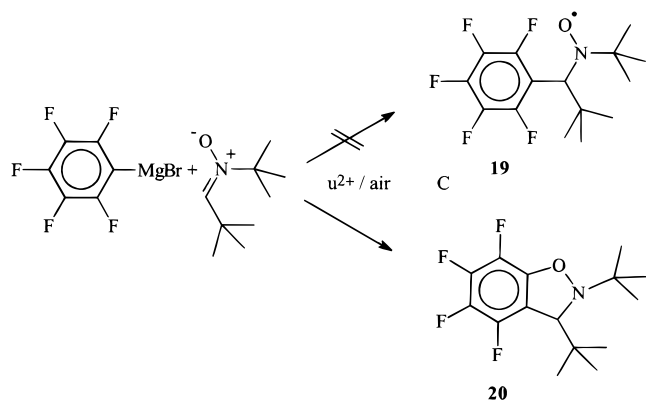
(21) Grimaldi, S.; Finet, J. P.; Zeghdaoui, A.; Tordo, P.; Benoit, D.; Gnanou, Y.; Fontanille, M.; Nicol, P.; Pierson, J. F. *Polym. Prepr*. **1997**, *38*, 651.

(22) Braslau, R.; Burrill, L. C., II; Siano, M.; Naik, N.; Howden, R. K.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445.
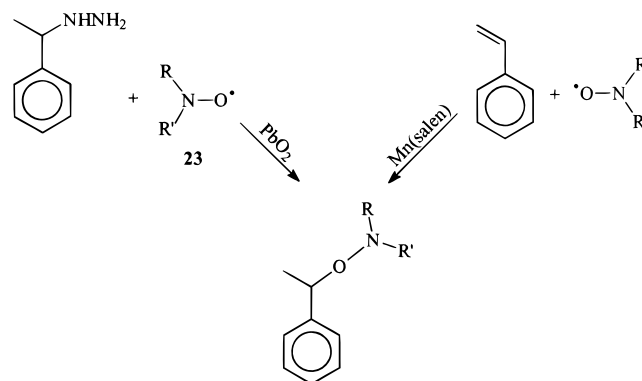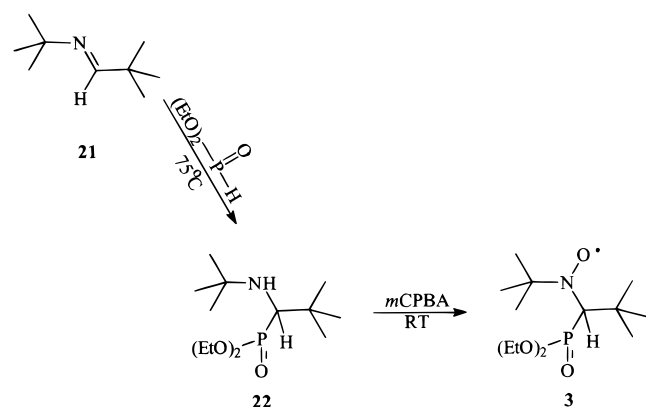
**Scheme 3**
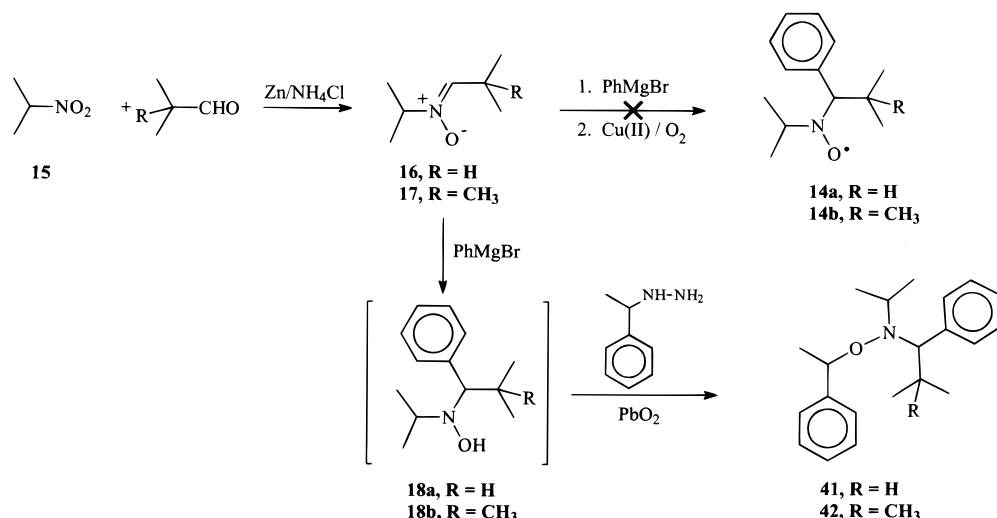


**Scheme 4**



**Scheme 6**



**Scheme 5**



as described by Hawker;[23] the alkoxyamines, **24**, were obtained in 40−70% yield after purification (Scheme 6). In the case of the chiral α-hydrogen nitroxides, mixtures of diastereomers were obtained which were not separated and in all subsequent experiments they were employed as diastereomeric mixtures.

A complete list of alkoxyamine structures employed in this study is shown in Figure 1. For evaluating this library of alkoxyamines, the initial screening procedure involved the polymerization of 200 equiv of styrene, or 200 equiv of *n*-butyl acrylate, in the presence of 1.0 equiv of the selected alkoxyamine

at 125 °C under nitrogen for 16 h. The polymeric product was then examined in terms of molecular weight, $M_n$, and polydispersity.

As can been seen from Table 1, the structure of the nitroxide has a significant effect on the ability of the alkoxyamines, **24**−**42**, to control the polymerization of both styrene and *n*-butyl acrylate. As expected from previous work, a larger range of alkoxyamine structures were able to control the polymerization of styrene, with most compounds giving experimental molecular weights within 10% of the theoretical molecular weights[24] and polydispersities (PD) between 1.14 and 1.21. The exceptions were the *cis*- and *trans*-isoindole derivatives, **30 a**−**b**, the doxyl derivatives, **32**, and **39**, and the α-phenyl-α-*tert*-butyl derivative, **31**. The lowest polydispersities and highest rates of polymerization were obtained for the 2,5-dimethyl-2,5-diphenylpyrrolidin-1-oxy derivative, **26**, and the α-phenyl-α-isopropyl derivatives **29**, **33**, **35**, **37**, and **38**. The results for **26** are consistent with the previous work of Puts and Sogah[25] who demonstrated that the use of DDPO as the mediating nitroxide leads to a faster rate of polymerization when compared to the use of TEMPO.

In comparison, the polymerization of *n*-butyl acrylate with the library of alkoxyamines, **24**−**42**, resulted in little, if any, control. With the exception of those of **29**, **33**, **35**, and **37**, all molecular weights were significantly different from the theoretical molecular weights, and polydispersities were 1.75 or greater. For **29** and **33**, the experimentally determined molecular weights

(23) Dao, J.; Benoit, D,; Hawker, C. J. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2161.

(24) Theoretical molecular weight is calculated from the molar ratio of styrene to initiator and is based on a conversion of 90%.
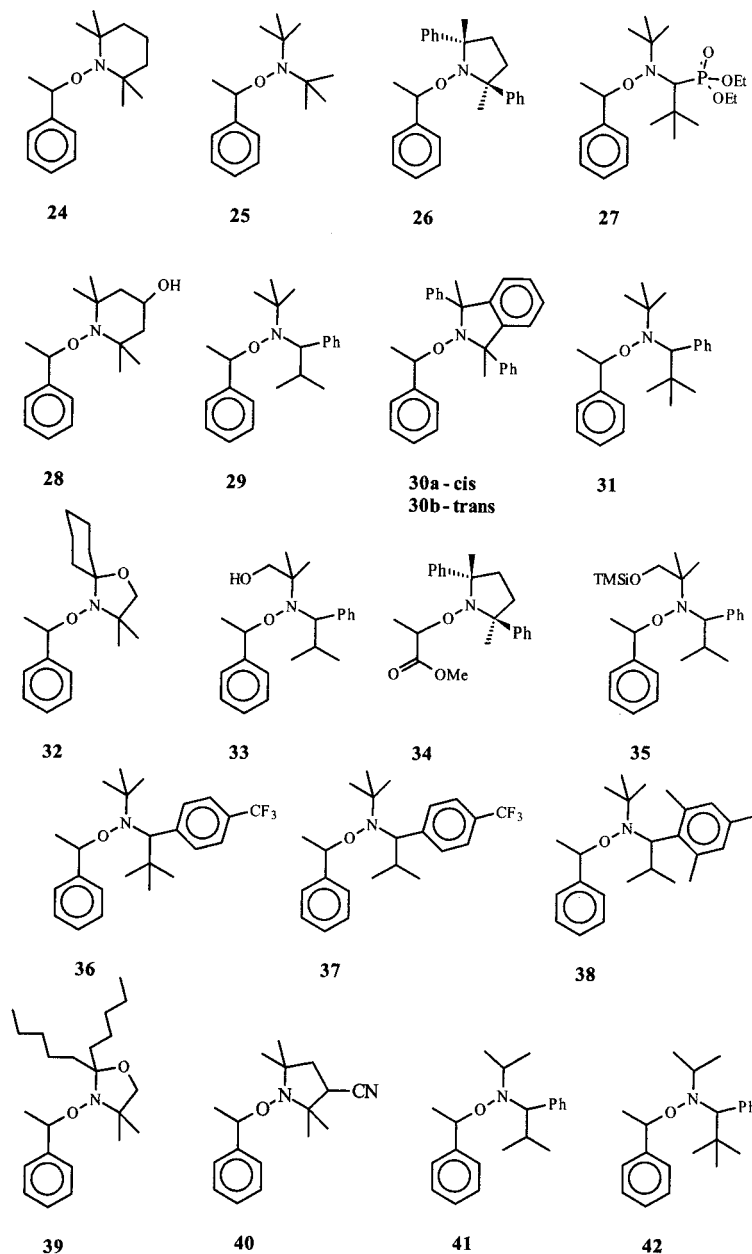(25) Puts, R. D.; Sogah, D. Y. *Macromolecules* **1996**, *29*, 3323.

**Figure 1.** Library of alkoxyamine structures evaluated as initiators for the living free radical polymerization of styrene and *n*-butyl acrylate.

of 26 500 (PD = 1.44) and 27 000 (PD = 1.40) were similar to the theoretical molecular weight of 24 000. These promising results coupled with the ready synthesis of **29** and **33** and their corresponding nitroxides prompted a full investigation into the ability of this family of alkoxyamines to control vinyl polymerization. The large-scale synthesis of **33** is especially attractive due to the low cost of 2-methyl-2-nitropropan-1-ol, **7**, isobutyrlaldehyde, and phenylmagnesium bromide.

Two interesting features that emerge from the above study are the insensitivity of the alkoxyamine to the presence, or absence, of a substituent $\beta$ to the nitrogen. The relative ability of **29**, **33**, and **35** to control the polymerization of styrene is approximately the same even though they have hydrogen, hydroxy, and trimethylsiloxy substituents in the $\beta$ position. It will be shown below that this relationship also holds for acrylate-based monomers and opens up the possibility of attaching functional moieties, such as chromophores to the nitroxide, or in the preparation of telechelic polymers.[20] In contrast, replacement of the *tert*-butyl group bonded to the nitrogen atom with an isopropyl group resulted in a dramatically reduced ability of

**41** and **42** to control polymerization. A rationale for these poor polymerization results can be made based on the following. Replacement of the *tert*-butyl group leads to a nitroxide with two α-hydrogens, which is inherently unstable, especially at elevated temperatures. This destabilization results in extensive decomposition of the nitroxide during the polymerization, and as a result the concentration of surviving nitroxide is now insufficient to mediate the polymerization. This explanation is partially supported by the observation that the nitroxide, **14a**, precursor of **41**, is less stable than the nitroxide, **14b**, precursor of **42**, which correlates with the substantially reduced ability of **41** to mediate polymerization when compared to **42**.

**Polymerization of Styrene**

The effectiveness of **29** or **33** for the living free radical polymerization of styrene was probed under bulk conditions at 123 °C with special attention being paid to molecular weight and polydispersity control. With no degassing or purification of the styrene, the polymerization was essentially complete within 18 h, and the molecular weight could be controlled up
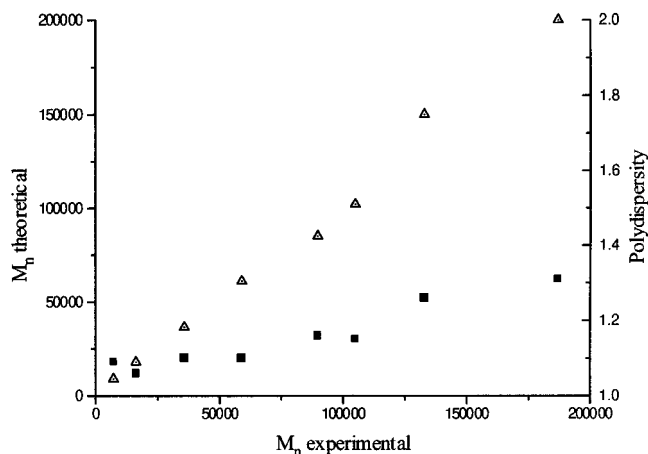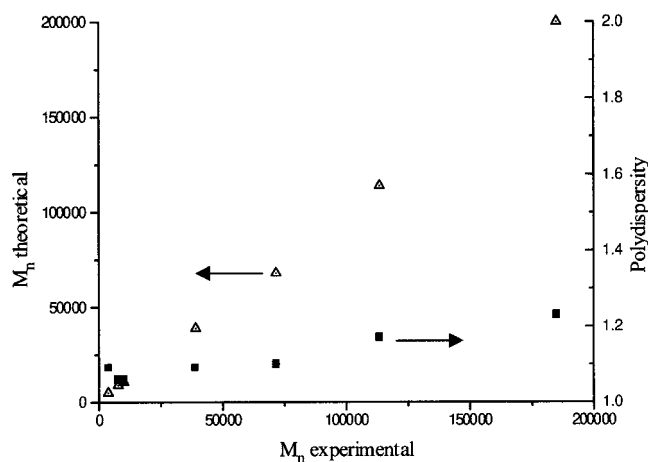
**Table 1.** Molecular Weight, $M_n$, and Polydispersity of Product Obtained from the Bulk Polymerization of 200 Equiv of Styrene, or *n*-Butyl Acrylate, with Various Alkoxyamines, at 123 °C

| | polystyrene | | poly(*n*-butyl acrylate) | |
|---|---|---|---|---|
| alkoxyamine | $M_n$ | polydispersity | $M_n$ | polydispersity |
| **24** | 22 000 | 1.16 | 3 000 | 2.45 |
| **25** | 22 500 | 1.18 | 9 000 | 1.8 |
| **26** | 26 500 | 1.17 | 32 000 | 2.05 |
| **27** | 28 000 | 1.21 | 22 000 | 1.9 |
| **28** | 21 000 | 1.2 | 7 500 | 1.75 |
| **29** | 21 500 | 1.14 | 26 500 | 1.44 |
| **30a** | 33 000 | 1.71 | 41 500 | 2.52 |
| **30b** | 22 000 | 1.49 | 26 000 | 2.25 |
| **31** | 30 500 | 1.39 | 12 000 | 1.75 |
| **32** | 50 000 | 1.72 | 57 000 | 3.81 |
| **33** | 22 000 | 1.14 | 27 000 | 1.40 |
| **34** | 23 000 | 1.23 | 28 000 | 1.90 |
| **35** | 22 500 | 1.15 | 26 500 | 1.45 |
| **36** | 24 000 | 1.19 | 32 500 | 1.55 |
| **37** | 22 000 | 1.16 | 29 000 | 1.50 |
| **38** | 25 000 | 1.15 | 27 500 | 1.55 |
| **39** | 42 000 | 1.65 | 61 000 | 2.80 |
| **40** | 20 000 | 1.25 | 45 000 | 1.95 |
| **41** | 38 000 | 1.68 | 95 000 | 2.10 |
| **42** | 25 000 | 1.30 | 38 000 | 1.70 |
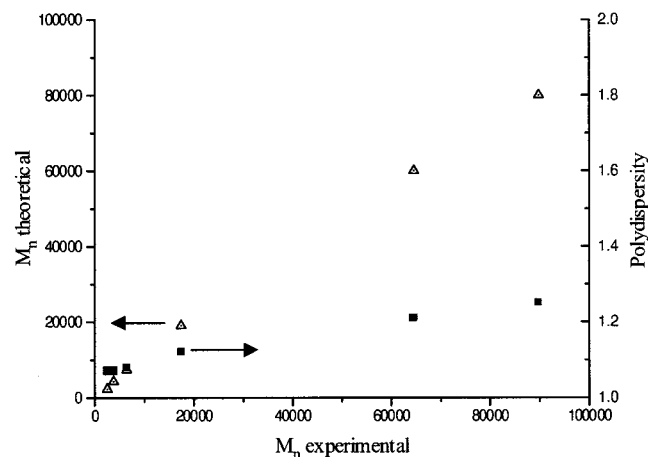


**Figure 2.** Evolution of experimental molecular weight, $M_n$, and polydispersity with theoretical MW for the polymerization of styrene and **33** at 123 °C for 18 h with no degassing or purification.



**Figure 3.** Evolution of experimental molecular weight, $M_n$, and polydispersity with theoretical MW for the polymerization of styrene and **29** at 123 °C for 12 h in the presence of acetic anhydride.



**Figure 4.** Evolution of experimental molecular weight, $M_n$, and polydispersity with theoretical MW for the polymerization of styrene and **29** at 123 °C for 4 h after purification of the monomer.

to 70 000 amu with polydispersities between 1.08 and 1.13 (Figure 2). A linear relationship between $\ln([M]_o/[M])$ vs time was also observed which indicates no detectable termination is occurring in this systems. The observed reduction in control for polymers with molecular weights in excess of 70 000 is similar to that observed originally for TEMPO[26] and is primarily due to the competing effects of autopolymerization, as well as termination at higher molecular weights.

Previously, a number of additives, such as camphor sulfonic acid or acetic anhydride, have been shown to accelerate TEMPO-based polymerization with a concomitant increase in the degree of control over the polymerization.[27] To investigate whether the same acceleration is observed with these new nitroxides, 2.0 equiv of acetic anhydride was added to the polymerization mixture of **29** and styrene. An effect similar to that observed for TEMPO was found, although the magnitude was reduced. Using this procedure, polymerization times were

decreased from 18 to 12 h, and a linear relationship between experimental and theoretical molecular weights, $M_n$, could now be obtained up to 100 000 amu (Figure 3). This reduced effect may actually be due to the different nature of the mediating nitroxide radical. While TEMPO is fairly stable and does not undergo a significant amount of decomposition during the course of the polymerization, the $\alpha$-hydrogen nitroxide, **1**, derived from **29** is susceptible to oxidation and nitrone formation. Therefore, additives such as acetic anhydride, or camphor sulfonic acid, which primarily affect the important autopolymerization step during TEMPO-mediated polymerization, may have a smaller effect in polymerizations mediated by **1** due to enhanced nitroxide decomposition pathways. The effect of oxidants or other radical sources, such as molecular oxygen, on the polymerization was then studied in detail. By carefully distilling and degassing the styrene monomer and performing the polymerization under argon in a sealed tube, a dramatic increase in the polymerization rate was observed with high conversions being obtained after ca. 4 h. In this case, the molecular weight control was excellent, up to 200 000 amu, and polydispersities were less than 1.10 up to 75 000 amu and then only increased slightly to 1.20−1.25 up to 200 000 amu (Figure 4). Interestingly, the effect of acetic anhydride on the degassed and purified system was minimal with no significant improvement in rate or degree of control being observed. A similar effect has been

(26) Hawker, C. J. *J. Am. Chem. Soc.* **1994**, *116*, 11314.
(27) Georges, M. K.; Veregin, R. P. N.; Kazmaier, P. M.; Hamer, G. K.; Saban, M. *Macromolecules* **1994**, *27*, 7228; Malmstrom, E. E.; Miller, R. D.; Hawker, C. J. *Tetrahedron* **1997**, *53*, 15225.

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**Table 2.** Bulk Polymerization of Styrene in the Presence of **29** and 2.0 equiv of Acetic Anhydride at 85 and 100 °C

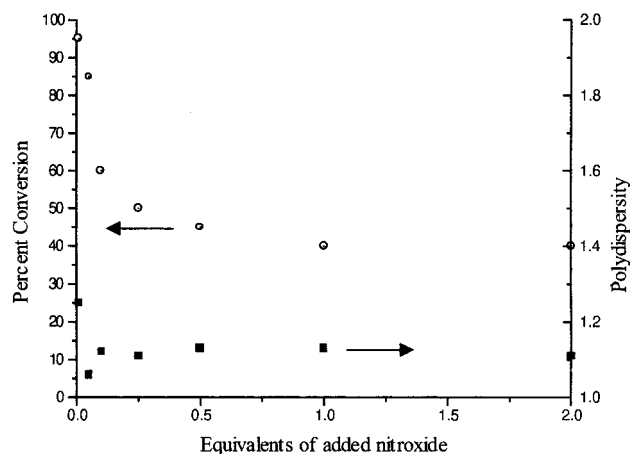| temperature | theoretical $M_n$ | experimental $M_n$ | polydispersity |
|---|---|---|---|
| 100 °C | 4 500 | 4 900 | 1.09 |
|  | 8 900 | 9 500 | 1.09 |
|  | 25 000 | 26 500 | 1.07 |
| 85 °C | 7 500 | 7 900 | 1.18 |
|  | 25 000 | 24 000 | 1.13 |

observed by Percec and Matyjasewski[28] during copper-mediated ATRP procedures, where the use of the monomer as received, coupled with sealing in air, results in a reduction in the rate of polymerization and a slight increase in polydispersity.

The efficient polymerization of styrene at the traditionally elevated temperature of 123 °C prompted an examination into the use of lower polymerization temperatures. Such a lowering in reaction temperature would not only be more energy efficient but would also permit the polymerization of temperature-sensitive monomers such as *p-tert*-butoxycarbonyloxystyrene which has found great utility as a photoresist component.[29] In the presence of 2.0 equiv of acetic anhydride, polymerization of styrene at both 100 and 85 °C led to well-defined materials with controlled molecular weights and low polydispersities (Table 2). Interestingly, the polydispersities obtained at 100°C were as low as those obtained at the more conventional 123°C, although the length of time required to reach high conversion (ca. 80–90%) increased to 24 h at 100°C and 90 h at 85°C. The 1:1 copolymerization of styrene and *tert*-butoxycarbonyloxystyrene was then conducted at 100°C to give a well-defined random copolymer ($M_n$ = 23 000, PD = 1.15) with no detectable loss of *tert*-butoxycarbonyl groups to give *p*-vinyl phenol units. In contrast, the polymerization at 125°C resulted in precipitation of the growing polymer chains to give a chloroform insoluble material which was shown to be a random copolymer of *p*-vinyl phenol and styrene with complete loss of the *tert*-butoxycarbonyl groups.

## Polymerization of Acrylates

The high degree of control afforded by **29** and **33** in the polymerization of styrene prompted a thorough investigation into the polymerization of other monomers, such as acrylates, etc. In our original screening process, a polydispersity of 1.44 was obtained for the polymerization of *n*-butyl acrylate; while this is less than the theoretical lower limit of 1.50 for a normal free radical polymerization, polydispersities of this magnitude cannot be considered controlled. A detailed investigation into the effect of polymerization conditions was therefore undertaken in an effort to decrease the polydispersity and increase the level of control during nitroxide-mediated polymerization of acrylates. The addition of additives, such as acetic anhydride, to the polymerization of butyl acrylate and **29** at 120 °C was initially examined. Significantly faster polymerization rates were observed, ca. 90% completion in 1–2 h; however, the control was poor with polydispersities being obtained in the range 1.50–2.20. This rapid polymerization is primarily due to the very high rate of polymerization of acrylate monomers, $k_p$ = 11 000 L mol$^{-1}$ s$^{-1}$ at 120 °C, in comparison to styrene at 120 °C, $k_p$ = 1800 L mol$^{-1}$ s$^{-1}$. To decrease the rate of polymerization and afford better control, varying amounts of free nitroxide, **1**, were

(28) Percec, V.; Kim, H.-J.; Barboiu, B. *Macromolecules* **1997**, *30*, 6702; Matyjaszewski, K.; Coca, S.; Gaynor, S. G.; Wei, M.; Woodworth, B. E. *Macromolecules* **1998**, *31*, 5967.

(29) Frechet, J. M. J.; Eichler, E.; Ito, H.; Willson, C. G. *Polymer* **1983**, *24*, 995; Willson, C. G.; Ito, H.; Frechet, J. M. J.; Tessier, T. G.; Houlihan, F. M. *J. Electrochem. Soc.* **1986**, *133*, 181.



**Figure 5.** Effect of added nitroxide, **1**, on the percent conversion and polydispersity of poly(butyl acrylate) prepared by the polymerization of *n*-butyl acrylate and **29** at 123 °C for 24 h.
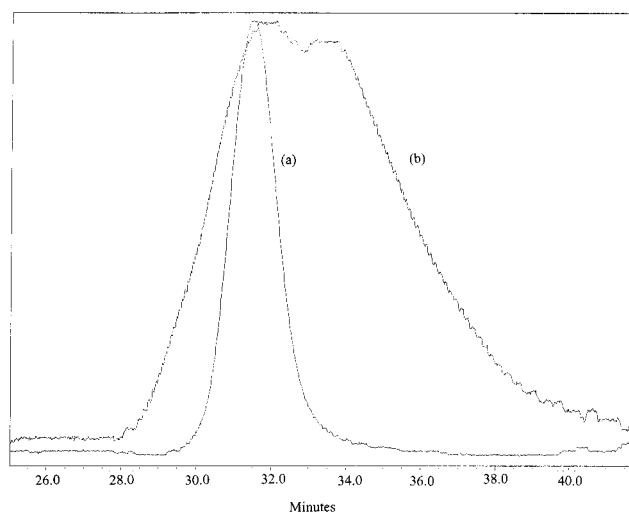


**Figure 6.** Comparison of GPC traces for poly(*n*-butyl acrylate) prepared by the polymerization of *n*-butyl acrylate (200 equiv) at 123 °C in the presence of (a) 1.0 equiv of **29** and 0.05 equiv of **1** and (b) 1.0 equiv of **24** and 0.05 equiv of TEMPO.

added to the polymerization mixture. Interestingly, the addition of free nitroxide has a marked effect on the degree of control afforded these polymerizations with significantly lower polydispersities being obtained. Addition of 0.01 equiv of **1** (with respect to the alkoxyamine **29**) resulted in a polydispersity of 1.25 and a degree of conversion of 95% after 16 h. Increasing the amount of added nitroxide gave lower polydispersities, 1.06–1.13, with a minimum of 1.06 being obtained for 0.05 equiv (Figure 5). However, the rate of polymerization was observed to slow upon addition of large amounts of free nitroxide, with ca. 40–45% conversion being obtained on addition of 0.5 equiv of **1** after 16 h. These results may be explained by the generation of an artificial persistent radical effect upon addition of excess nitroxide, similar to the persistent radical effect described by Fischer.[3a] It can therefore be concluded that the alkoxyamine, **29**, can indeed control the polymerization of acrylates and the optimal reaction conditions involve the addition of 0.05 equiv of free nitroxide. This feature can be better appreciated if the GPC traces for poly(butyl acrylate) grown in the presence of **29** and **1** is compared to poly(butyl acrylate) grown in the presence of TEMPO (Figure 6). It should also be noted that the polymerization of acrylates may also be conducted at lower temperatures (ca. 95–100 °C)
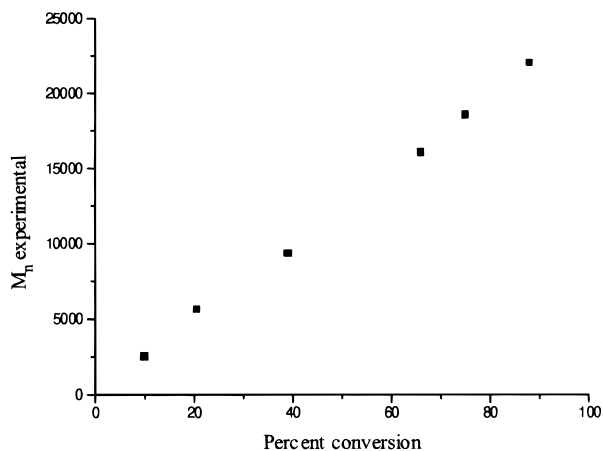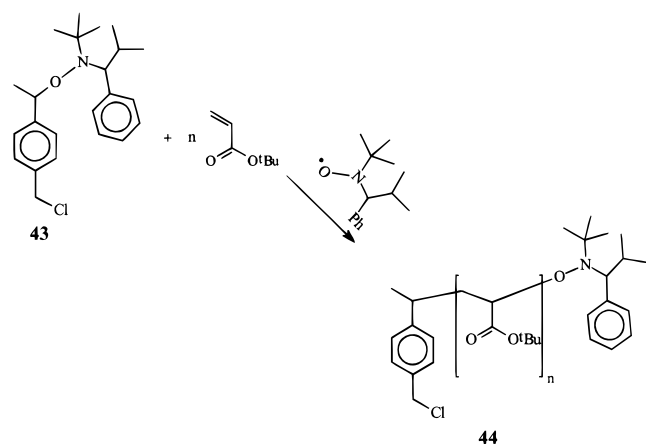
**Figure 7.** Evolution of molecular weight, $M_n$, with percent conversion for the polymerization of *n*-butyl acrylate (250 equiv) in the presence of **29** (1.0 equiv) and **1** (0.05 equiv) at 123 °C for 16 h.

**Scheme 7**





**Figure 8.** $^1$H NMR spectrum of oligomeric poly(*tert*-butyl acrylate), **44**, prepared by the polymerization of *tert*-butyl acrylate (25 equiv) at 123 °C in the presence of 1.0 equiv of **43** and 0.05 equiv of **1**.



**Figure 9.** Relationship between experimental molecular weight, $M_n$, and theoretical molecular weight for the polymerization of *n*-butyl acrylate in the presence of **29** (1.0 equiv) and **1** (0.05 equiv) at 123 °C for 16 h.

with similar levels of control, although, as with the styrene, the time required to reach high conversion is increased to 48 h.

The living nature of this new bimolecular alkoxyamine/ nitroxide-initiating system was then probed by polymerizing 250 equiv of *n*-butyl acrylate with 1.0 equiv of **29** and 0.05 equiv of **1** at 120 °C under argon. As can be seen in Figure 7, the evolution of molecular weight with conversion is linear, and the polydispersity in each case was 1.05–1.10, which is fully consistent with a controlled or living free radical polymerization. A linear relationship between ln([M]$_o$/[M]) vs time was also observed which indicates no detectable termination is occurring in this system. Initiator efficiency was examined by preparing short oligomeric chains from the chloromethyl functionalized initiator, **43** (Scheme 7). For example, a mixture of 25 equiv of *tert*-butyl acrylate, 1.0 equiv of **43**, and 0.05 equiv of **1** were heated at 125 °C under argon for 24 h to give the oligomer, **44**, which was shown to have a molecular weight, $M_n$ of 2800 amu, and a polydispersity of 1.09 after purification. As shown in Figure 8, the $^1$H NMR spectrum of **44** clearly shows the resonance for the chloromethyl group of the initiating chain end at 4.48 ppm and the α-hydrogen of the nitroxide chain end at 3.25 ppm. Integration of these resonances reveals a ca. 1:1 ratio and gives a molecular weight, $M_n$, of 2700 amu which is consistent with controlled growth and no detectable termination. Interestingly, the absence of resonances at 6.7 and 5.8 ppm for an alkene-terminated chain, the result of nitroxide elimination, further supports a living process.

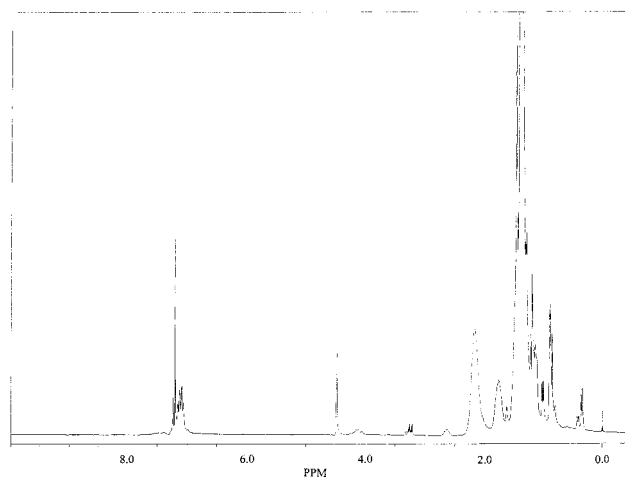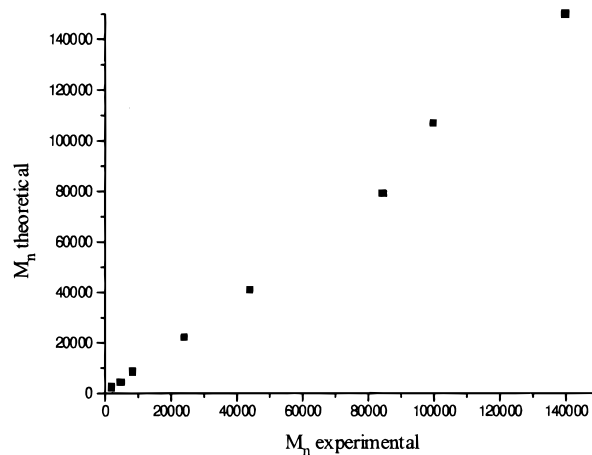One of the prime advantages of using alkoxyamines as unimolecular initiators is the accurate control over molecular weight that these systems afford. This control over molecular weight has been amply demonstrated for styrenic-based systems and for acrylate-based systems using ATRP.[30] The ability of these new alkoxyamines, such as **29**, to control molecular weight was examined under the conditions defined above. On the basis of the assumption that one polymer chain is initiated per alkoxyamine molecule and the length of the polymer chain is dictated by the molar ratio of monomer to alkoxyamine, with no contribution from added nitroxide, the observed relationship between theoretical and experimental molecular weight is excellent.[31] For molecular weights below 50 000, the polydispersity is low, ca. 1.05–1.10, and only increases slightly, ca. 1.10–1.30, at higher molecular weights (Figure 9). The level of degree of control afforded by **29** for the nitroxide-mediated polymerization of acrylates is therefore comparable to ATRP systems, as well as the recently introduced RAFT procedures.[10]

## Random Copolymers

In comparison with other living techniques, two of the unique features of living free radical polymerizations is their compat-

(30) Qui, J.; Matyjaszewski, K. *Macromolecules* **1997**, *30*, 5176.

(31) All experimental molecular weights, except those for random and block copolymers, were determined using gel permeation chromatography using the appropriate standards.
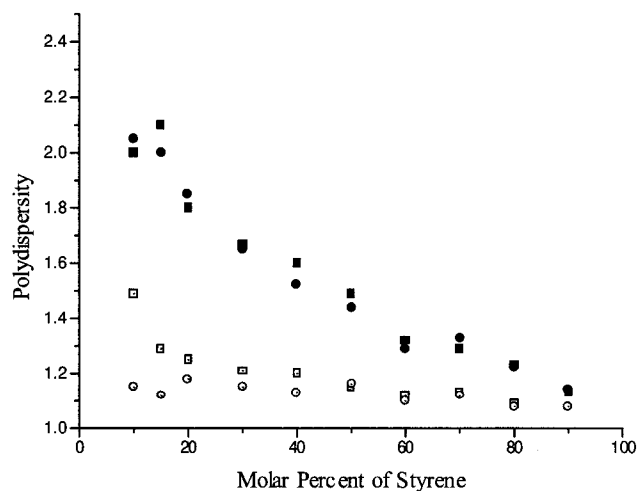
**Figure 10.** Relationship between polydispersity of the resulting random copolymers and mol % of styrene in the feed mixture for the copolymerization of (i) styrene and *n*-butyl acrylate (■), (ii) styrene and methyl methacrylate (●) mediated by TEMPO-based systems, **24**, compared with (iii) styrene and *n*-butyl acrylate (○), and (iv) styrene and methyl methacrylate (□) mediated by **29** or **33**.

ibility with a wide range of functional groups, coupled with their ability to prepare well-defined random copolymers.[32] While it has been shown that TEMPO-mediated living free radical polymerizations can produce random copolymers of styrene with either acrylate or methacrylate monomers,[11] the degree of control drops significantly as the mole percentage of styrene decreases below 60%. The ability of **29** to mediate the homopolymerization of acrylates should alleviate this problem and permit a much greater range of well-defined random copolymers to be prepared.

In examining this possibility, the polymerization of styrene and butyl acrylate mixtures in the presence of **29** and acetic anhydride at 125 °C was conducted. In contrast to the results obtained with TEMPO, both molecular weight and polydispersity control was excellent, with all of the molecular weights being within 10% of the theoretical molecular weights and polydispersities between 1.08 and 1.20. Given the control afforded by **29** in the homopolymerization of both styrenics and acrylates, this ability to prepare well-defined random copolymers is expected. However a more surprising result was obtained when the random copolymerization of styrene and methyl methacrylate was examined. In this case, well-defined random copolymers could be obtained up to very high methyl methacrylate ratios (ca. 85%), and only at methacrylate ratios of greater than 90% did the polydispersity become greater than 1.50. Significantly, no resonances were observed in the 5.50–6.20 ppm region, characteristic of alkene-terminated chains.

To better appreciate these results, the polydispersities obtained for the random copolymerization of styrene/butyl acrylate and styrene/methyl methacrylate mixtures initiated by **29** were compared with those for TEMPO-based systems. Significantly greater control is observed with **29** compared to TEMPO at essentially all molar ratios and becomes exacerbated at molar percentages of styrene of less than 60% (Figure 10).

The linear nature of the relationship between molecular weight, $M_n$, and conversion, coupled with the ability to readily control the molecular weights of these random copolymers by

(32) Kotani, Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **1998**, *31*, 5582; Haddleton, D. M.; Crossman, M. C.; Hunt, K. H.; Topping, C.; Waterson, C.; Suddaby, K. G. *Macromolecules* **1997**, *30*, 3992; Greszta, D.; Matyjaszewski, K. *Polym. Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **1996**, *37* (1), 569.

**Table 3.** Homopolymerization of Acrylonitrile* and *N,N*-dimethylacrylamide Using **29** as an Initiator at 120 °C

| monomer | ratio of monomer/**29** | $M_n$ | polydispersity[a] |
|---|---|---|---|
| acrylonitrile | 50/1 | 4 500 | 1.12 |
| | 200/1 | 22 000 | 1.16 |
| | 500/1 | 55 000 | 1.13 |
| *N,N*-dimethylacrylamide | 50/1 | 4 000 | 1.15 |
| | 100/1 | 8 500 | 1.12 |
| | 200/1 | 21 500 | 1.14 |
| | 500/1 | 48 000 | 1.21 |

[a] Polymerization of acrylonitrile was conducted in a 50 wt % DMF solution; polydispersity and $M_n$ of poly(acrylonitrile) samples were determined by GPC using DMF as solvent.
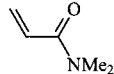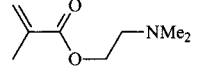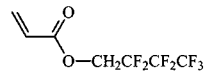
simply varying the molar ratio of **29** and the total monomer concentration, confirms the living nature of these random copolymerizations. For example, the molecular weight, $M_n$, of a series of 3:7 styrene/*n*-butyl acrylate random copolymers was within 10% of the theoretical value for molecular weights in the range of 2000 to 100 000.

In an effort to further extend the scope of nitroxide-mediated living free radical polymerization, the random copolymerization of acrylates and methacrylates was studied by means of a procedure similar to that for the homopolymerization of acrylates. For example, a mixture of *tert*-butyl acrylate (100 equiv) and methyl methacrylate (100 equiv) was heated at 125 °C in the presence of 1.0 equiv of **29** and 0.05 equiv of the free nitroxide **1**. The copolymer obtained was shown to be a statistical random copolymer by ^{1}H NMR spectroscopy and analysis by GPC, $M_n$ = 22 000, PD = 1.24, demonstrating that the level of control was similar to that found above for the styrene/methacrylate random copolymers. This was further confirmed by examination of a wide range of copolymer ratios which showed that well-defined materials (PD < 1.35) were obtained for up to 80% of methyl methacrylate, and only at higher methacrylate ratios did polydispersities become greater than 1.50. It should be noted, however, that the level of control at all molar ratios was significantly greater than for the copolymerization of styrene and methyl methacrylate mediated by TEMPO, while the copolymerizations of acrylates and methyl methacrylate by TEMPO fail to give polymers.

**Acrylamides, Acryonitrile and other Functionalized Monomers.** The ability of **29** to control the homopolymerization of acrylates suggested that this system may be applicable to an even wider selection of monomer units, similar to ATRP procedures. If this was indeed the case, many of the challenges and problems typically associated with nitroxide-mediated polymerizations would be overcome. Brittain has recently reported[33] the polymerization of *N,N*-dimethylacrylamide using TEMPO as the mediating radical and obtained poly(acrylamide) derivatives with polydispersities ranging from 1.55 to greater than 2.0. In contrast, the polymerization of *N,N*-dimethylacrylamide in the presence of **29** and 0.05 equiv of **1** proved to be a well-controlled process leading to poly(*N,N*-dimethylacrylamide) with polydispersities ranging from 1.12 to 1.21. Similarly, the homopolymerization of acrylonitrile was found to be a controlled process when initiated by **29**, both in the absence and presence of excess nitroxide. In both cases the molecular weight could be controlled from 4000 to 50 000 as shown in Table 3. The ability to homopolymerize or copolymerize acrylonitrile to high molecular weight is in contrast to the results obtained with ATRP systems which are limited to molecular

(33) Li, D.; Brittain, W. J. *Macromolecules* **1998**, *31*, 3852.

**Table 4.** Polydispersity and Polystyrene Equivalent Molecular Weights, $M_n$, for the Bulk Random Copolymerization of Styrene and a Variety of Functionalized Monomers (200 equiv) in the Presence of **29** at 120 °C

| Comonomer | Ratio of Sty/Comonomer | $M_n$ | Polydispersity |
|---|---|---|---|
| (acrylonitrile, —CN) | 90/10 | 21 500 | 1.09 |
| | 70/30 | 22 000 | 1.12 |
| | 50/50 | 22 500 | 1.14 |
| | 30/70 | 19 000 | 1.06 |
| (acrylamide, NMe₂) | 70/30 | 20 000 | 1.1 |
| | 50/50 | 18 000 | 1.11 |
| | 30/70 | 19 500 | 1.14 |
| (methacrylate, O—CH₂CH₂—NMe₂) | 90/10 | 19 500 | 1.09 |
| | 80/20 | 20 000 | 1.08 |
| | 50/50 | 20 500 | 1.12 |
| (acrylate, O—CH₂CF₂CF₂CF₃) | 90/10 | 19 500 | 1.07 |
| | 70/30 | 17 000 | 1.12 |
| | 50/50 | 18 000 | 1.22 |

**Table 5.** Polydispersity and Polystyrene Equivalent Molecular Weights, $M_n$, for the Bulk Random Copolymerization of Butyl Acrylate and a Variety of Functionalized Monomers (200 equiv) in the Presence of **29** and **1** (0.05 Equiv) at 120 °C

| Comonomer | Ratio of Acrylate/Comonomer | $M_n$ | Polydispersity |
|---|---|---|---|
| (acrylonitrile, —CN) | 90/10 | 17 000 | 1.18 |
| | 80/20 | 14 500 | 1.15 |
| | 70/30 | 16 500 | 1.13 |
| | 50/50 | 18 000 | 1.09 |
| | 30/70 | 18 000 | 1.1 |
| | 10/90 | 17 000 | 1.15 |
| (acrylic acid, OH) | 95/5 | 19 500 | 1.12 |
| | 90/10 | 21 500 | 1.1 |
| | 80/20 | 22 000 | 1.26 |
| | 50/50 | 20 000 | 1.55 |
| (acrylamide, NMe₂) | 70/30 | 15 500 | 1.18 |
| | 50/50 | 14 500 | 1.19 |
| | 30/70 | 17 000 | 1.15 |
| (acrylate, O—CH₂CH₂—OH) | 95/5 | 19 000 | 1.14 |
| | 90/10 | 18 000 | 1.19 |
| | 50/50 | 18 000 | 1.30 |
| (acrylate, O—CH₂CF₂CF₂CF₃) | 90/10 | 19 500 | 1.12 |
| | 50/50 | 19 000 | 1.25 |
| (acrylate, O—CH₂CH₂OCH₂CH₂OCH₃) | 90/10 | 20 000 | 1.17 |
| | 80/20 | 19 000 | 1.15 |
| | 50/50 | 17 000 | 1.35 |
| (glycidyl acrylate, epoxide) | 95/5 | 20 000 | 1.16 |
| | 90/10 | 21 000 | 1.18 |
| | 80/20 | 23 000 | 1.18 |
| | 50/50 | 28 000 | 1.52 |

weights of less than 15 000.[34] Presumably this is due to the slow deactivation of the copper catalyst with poly(acrylonitrile) with time and demonstrates that the lack of a metal catalyst requirement with nitroxide-mediated procedures is beneficial for certain systems.
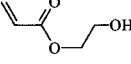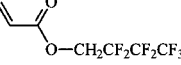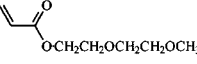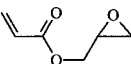
## Functionalized Monomers

The ability to polymerize functionalized monomers under controlled conditions is a major advantage of living free radical procedures.[7,35] The demonstrated capacity of **29** to polymerize a wide variety of monomer families suggested that it might also be compatible with reactive functional groups such as carboxylic acids, epoxides, etc. This feature was probed by copolymerizing mixtures of styrene, or butyl acrylate, with a variety of reactive monomer units. As shown in Tables 4 and 5, a high degree of control was maintained over the random copolymerization even in the presence of a significant amount of the reactive monomer unit, ca. 1:1. At low levels of incorporation, ca. <25%, the influence of functionalized monomers on the level of control was negligible. For a range of functional groups, from basic amine, acidic carboxylate, and fluorocarbon to hydrophilic groups, low polydispersity and well-defined polymer were obtained. Only at high loading levels (ca. 50%) and in select cases, such as acrylic acid and glycidyl acrylate, did the polydispersities rise to 1.5−1.55. Similar difficulties in the polymerization of acrylic acid were observed in ATRP procedures by Matyjaszewski and are again due to catalyst deactivation by the coordinating ability of the monomer.[34]

From these experiments it can be concluded that the alkoxyamines **29** and **33** are capable of controlling the homo- and copolymerization of a wide range of monomer units, i.e., styrenics, acrylates, acrylamides, and acrylonitrile, while at the same time being compatible with a variety of functional groups.

## Block Copolymers

The presence of dormant initiating centers at the chain end/s of linear polymers prepared by both nitroxide-mediated and ATRP procedures provides unique opportunities for the preparation of block copolymer structures, and this feature has been exploited by numerous groups.[36] While the block copolymers available from living free radical procedures may not be as well defined as the best examples available from anionic techniques, they have the advantage of greater availability and a significantly greater tolerance of functional groups. Technological applications that have been examined for these block copolymer include dispersants for pigments,[37] precursors to shell cross-linked nanoparticles for drug delivery,[38] supports for combinatorial chemistry,[39] and resist materials for photolithography.[40]

In exploiting these opportunities, nitroxide-mediated systems have lagged behind ATRP-based systems, primarily due to the more limited choice of monomer units that could be efficiently homopolymerized. The ability of **29** to overcome this limitation opens up the possibility of preparing a wide range of block copolymer structures using nitroxide-mediated procedures.

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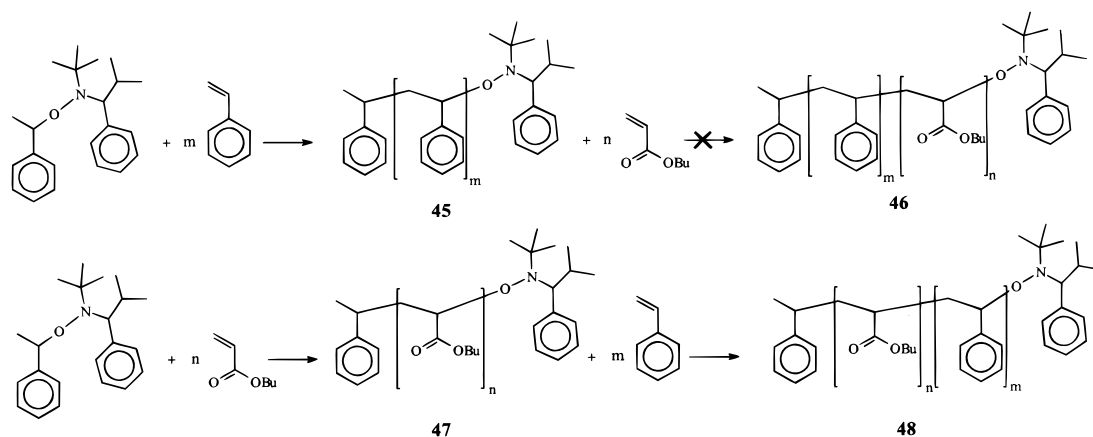
**Scheme 8**



**Table 6.**  Molecular Weight, $M_n$, and Polydispersity for Poly(*n*-butyl Acrylate)-*b*-polystyrene Block Copolymers, **48**, Prepared Using **29** under Bulk Conditions at 120 °C

| poly(*n*-butyl acrylate) starting block | | | P(*n*-BA)-*b*-PSt block copolymer[b] | |
|---|---|---|---|---|
| $M_n$ | polydispersity | composition[a] Sty/*n*-BA | $M_n$ | polydispersity |
| 2 100 | 1.08 | 85/15 | 12 500 | 1.06 |
| 4 500 | 1.05 | 80/20 | 26 000 | 1.09 |
| 7 800 | 1.08 | 85/15 | 42 000 | 1.07 |
| 7 800 | 1.08 | 80/20 | 37 000 | 1.12 |
| 7 800 | 1.08 | 70/30 | 31 000 | 1.09 |
| 7 800 | 1.08 | 60/40 | 21 000 | 1.07 |
| 7 800 | 1.08 | 50/50 | 17 500 | 1.1 |
| 7 800 | 1.08 | 43/57 | 14 500 | 1.12 |
| 7 800 | 1.08 | 32/68 | 11 000 | 1.09 |
| 23 500 | 1.09 | 73/27 | 85 000 | 1.19 |
| 23 500 | 1.09 | 57/43 | 68 000 | 1.16 |
| 23 500 | 1.09 | 40/60 | 44 000 | 1.13 |
| 32 500 | 1.06 | 70/30 | 111 000 | 1.16 |
| 32 500 | 1.06 | 42/58 | 61 000 | 1.13 |
| 32 500 | 1.06 | 33/67 | 49 000 | 1.09 |
| 76 500 | 1.1 | 73/27 | 205 000 | 1.32 |
| 76 500 | 1.1 | 50/50 | 145 000 | 1.28 |
| 76 500 | 1.1 | 30/70 | 105 000 | 1.19 |

[a] Determined by $^1$H NMR spectroscopy. [b] Polystyrene equivalent molecular weights.

Initially, a starting polystyrene block, **45** ($M_n$ = 4500 amu, PD = 1.08), was prepared from **29** and 50 equiv of styrene in the presence of acetic anhydride and purified by repeated precipitation into methanol. A second poly(*n*-butyl acrylate) block was then grown by dissolution of **45** in butyl acrylate (500 equiv), addition of 0.05 equiv of nitroxide, **1**, followed by heating at 123 °C under argon. As evidenced by the GPC traces for the block copolymer, **46**, versus the starting material, **45**, controlled growth is achieved with no evidence of homopolymer contamination. However, when higher molecular weight starting polystyrene blocks were used, or when a similarly sized polyacrylate block was grown, there was a substantial low molecular weight shoulder observed. The exact nature of this shoulder, whether it is unreacted or terminated starting polystyrene block, is unknown. Attempts to overcome this unexpected lack of reactivity by the addition of solvent, etc. were unsuccessful.

The difficulty in preparing block copolymers by initially growing a polystyrene block followed by growth of a second polyacrylate block prompted an investigation of the reverse strategy. Interestingly, this reverse strategy proved to be extremely successful and allowed the preparation of well-defined block copolymers with levels of control comparable to those of ATRP procedures. In this strategy (see Scheme 8), an alkoxyamine-functionalized poly(*n*-butyl acrylate) block, **47** ($M_n$ = 7800, PD = 1.08), was initially grown and then used to polymerize 200 equiv of styrene in the presence of acetic anhydride (1.0 equiv) at 123 °C under argon for 8 h. This resulted in 92% conversion and gave the block copolymer, **48**, analysis of which revealed the expected increase in molecular weight ($M_n$ = 28 000, PD = 1.09), while the polydispersity remained very low and there was no detectable amount of unreacted starting poly(acrylate) block as analyzed by a combination of GPC and HPLC. techniques (Figure 11). This block copolymer formation proved to be a general procedure and permitted a wide compositional range of poly(*n*-butyl acrylate)-*b*-polystyrene block copolymers to be prepared with accurate control of molecular weight up to 200 000 amu and polydispersities typically in the range of 1.06−1.19 (Table 6).

The same chemistry can be used to prepare functionalized block copolymers. For example, a starting block can be prepared from heptafluorobutyl acrylate and then a second nonflourinated block grown by polymerization of *n*-butyl acrylate. In this case the low solubility of the starting fluorinated block in *n*-butyl acrylate was overcome by the addition of an equivalent amount, by weight, of hexafluorobenzene to the polymerization mixture. While the addition of a cosolvent reduced the polymerization rate (ca. 30 h for high conversion), growth was still controlled and a well-defined block copolymer, **49**, $M_n$ = 116 000, PD = 1.18, was obtained.
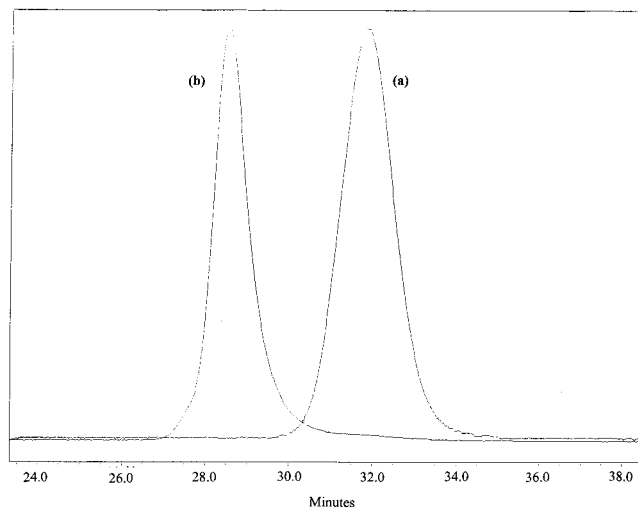
*Alkoxyamine for Controlled Polymerizations*

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**Figure 11.** Comparison of GPC traces for (a) the starting poly(*n*-butyl acrylate) polymer, **47**, and (b) the poly(*n*-butyl acrylate)-*b*-polystyrene block copolymer, **48**, obtained after chain extension with styrene.

## Conclusion

By the synthesis of a library of different nitroxides and their associated alkoxyamines, the α-hydrido family of unimolecular initiators, in particular **29** and **33**, has been identified as universal initiators for nitroxide-mediated living free radical polymerizations. In comparison with traditional TEMPO-based systems, their performance is significantly improved and permits the controlled polymerization of a wide variety of monomer families. Acrylates, acrylamides, and acrylonitrile-based monomers can now be polymerized with accurate control of molecular weights and polydispersities as low as 1.06. The versatile nature of these initiators can also be used to control the formation of random and block copolymers from a wide selection of monomer units containing reactive functional groups, such as amino, carboxylic acid, and glycidyl. The universal nature of these initiators overcomes many of the limitations typically associated with nitroxide-mediated systems and leads to a level of versatility approaching ATRP-based systems.

## Experimental Section

**General**. All reactions were run under $N_2$ unless noted. Solvents were dried as follows: THF and toluene were distilled under $N_2$ from sodium benzophenone, and $CH_2Cl_2$ was distilled from calcium hydride. *m*-Chloroperbenzoic acid was purified by the procedure of Fieser and Fieser. Analytical thin-layer chromatography (TLC) was performed on commercial Merck plates coated with silica gel GF254 (0.25 mm thick). Silica gel for flash chromatography was either Merck Kieselgel 600 (230−400 mesh) or Universal Scientific Inc. silica gel 63-200. Nuclear magnetic resonance (NMR) spectroscopy was performed on a Bruker ACF 250, AM 500 MHz, or Varian Unity 500 MHz NMR spectrometer using deuterated chloroform (CDCl$_3$) as solvent and the internal solvent peak as the reference. ESR spectra were measured on a Bruker ESP 300 spectrometer operated in continuous wave (CV) mode with a $TE_{102}$ rectangular cavity. Gel permeation chromatography (GPC) was carried out on a Waters chromatograph (four Waters Styragel HR columns HR1, HR2, HR4, and HR5E in series) connected to a Waters 410 differential refractometer with THF as the carrier solvent. IR spectra were recorded in CDCl$_3$ solution. Mass spectra were obtained at the University of Illinois using magic bullet or fast atom bombardment (FAB); electrospray mass spectroscopy (ESMS) was taken at University of California at Santa Cruz using a Quattro II Triplequadrupole mass spectrometer. Melting points are uncorrected. The following alkoxyamines has been reported previously, **24**,[6] **25**,[4] and **28**.[6]

***N*-tert-Butyl-α-*iso*-propylnitrone (5a).** A mixture of 2-methyl-2-nitropropane, **6** (51.5 g, 500 mmol), isobutyraldehyde (36.0 g, 500

mmol), ammonium chloride (29.4 g, 550 mmol), and 1000 mL of water were cooled to 0 °C in an ice-bath, and 500 mL of diethyl ether was then added to partially dissolve the crystallized 2-methyl-2-nitropropane. Zinc powder (130 g, 2.00 mol) was added in small portions over 1 h with stirring. After 8 h, the mixture was filtered through a sintered glass filter and the residue washed three times with 300 mL of methanol. The product was extracted four times with 500 mL of dichloromethane. The organic layers were combined and washed with 800 mL of brine, dried over magnesium sulfate, and concentrated in vacuo to give 59.9 g (84% yield) of crude nitrone **5a** as a colorless, low-melting solid, partially crystallized at room temperature. TLC 10:1 ethyl acetate/methanol, molybdenum stain, $R_f = 0.49$. $^1$H NMR (250 MHz, CDCl$_3$) δ 6.52 (s, 1H), 2.10 (m, 1H), 1.42 (d, 6H), 1.21 (s, 9H); $^{13}$C NMR (63 MHz, CDCl$_3$) δ 139.55, 69.21, 30.67, 28.49, 26.10.

**2,2,5-Trimethyl-4-phenyl-3-azahexane-3-nitroxide (1).** *N*-tert-butyl-α-*iso*-propylnitrone (**5a**) (66.0 g, 461 mmol) was dissolved in 500 mL of THF and the solution cooled to 0 °C. A 3.0 M solution of phenylmagnesium bromide (310 mL, 920 mmol) in diethyl ether was added by cannula at this temperature over 5 min. During the addition some precipitate formed. The mixture was allowed to warm to room temperature. After 12 h, excess Grignard reagent was decomposed by the addition of 100 mL of concentrated ammonium chloride solution followed by 300 mL of water until all solids had dissolved. The organic layer was separated, and the aqueous layer was extracted with 500 mL of diethyl ether. The organic layers were combined, dried over magnesium sulfate, filtered, and concentrated, and the residue was treated with a mixture of 2000 mL of methanol, 150 mL of concentrated NH$_4$OH, and 4.59 mg (23 mmol) of Cu(OAc)$_2$ to give a pale yellow solution. A stream of air was bubbled through the yellow solution until it became dark blue (5−10 min). This was concentrated and the residue dissolved in a mixture of 2000 mL of chloroform, 500 mL of concentrated NaHSO$_4$ solution, and 2000 mL of water. The organic layer was separated, and the aqueous layer was extracted with 500 mL of chloroform. The organic layers were combined and washed with 600 mL of saturated sodium bicarbonate solution, dried over magnesium sulfate, and concentrated in vacuo to give 101.6 g of crude nitroxide. The nitroxide was then purified by flash column chromatography (20:1 hexane/ethyl acetate) to afford 72.6 g (71% yield) of pure **1** as an orange oil, which crystallized at temperatures below 4 °C. TLC 16:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.49$; $^1$H NMR (250 MHz, CDCl$_3$, in the presence of pentafluorophenyl hydrazine) δ 7.60−7.25 (m, 5H, Ph), 3.41 (d, 1H, *J* = 6.5 Hz), 2.28 (m, 1H), 1.44 and 0.97 (s, 9H), 1.20 and 0.58 (d, 6H, *J* = 6.8 Hz); $^{13}$C NMR (62.5 MHz, CDCl$_3$) in the presence of pentafluorophenyl hydrazine, δ 154.26, 142.06, 141.20, 136.02, 129.50, 128.77, 128.43, 127.82, 127.25, 126.61, 73.37, 71.31, 63.30, 59.10, 31.51, 31.23, 30.19, 26.85, 21.54, 20.55, and 18.48.

***N*-tert-Butyl-α-*tert*-butylnitrone (51).** The nitrone **51** was prepared from pivalaldehyde as described above and was obtained in 62% yield as a colorless solid; TLC 10:1 ethyl acetate/methanol, molybdenum stain, $R_f = 0.76$. $^1$H NMR (250 MHz, CDCl$_3$) δ 6.52 (s, 1H), 1.42 (s, 9H), 1.21 (s, 9H); $^{13}$C NMR (63 MHz, CDCl$_3$) δ 139.74, 69.63, 32.54, 28.24, 26.18.

**2,2,5,5-Tetramethyl-4-phenyl-3-azahexane 3-nitroxide (52).** The nitroxide **52** was prepared from *N*-tert-butyl-α-*tert*-butylnitrone, **51** (800 mg, 5.09 mmol), as described above and was obtained as an orange oil (83% yield), which crystallized at temperatures below 4 °C. TLC: 16:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.48$.

**2,2,5-Trimethyl-4-(4-trifluoromethylphenyl)-3-azahexane-3-nitroxide (53).** The trifluoromethyl-substituted nitroxide, **53**, was prepared from *p*-trifluoromethyl phenylmagnesium bromide and *N*-tert-butyl-α-*iso*-propylnitrone, **5a**, using the general procedure outlined above. The nitroxide, **53**, was purified by flash column chromatography, eluting with 16:1 hexane/ethyl acetate and was obtained as an orange solid (74% yield); TLC 16:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.34$; mp 80−81 °C; IR(CDCl$_3$) 2977, 1617, 1325, 1168, 1130, 1068 cm$^{-1}$; ESR (CH$_2$Cl$_2$) doubled triplet, $a_n$ = 15.249 G, $a_h$ = 2.639 G; MS (FAB) *m/z* 288 ([M]$^+$, 36), 274 (28), 232 (100), 201 (19); HRMS exact mass calcd for [M$^+$] C$_{15}$H$_{21}$F$_3$NO 288.1576, found 288.1576; $^1$H NMR (250 MHz, CDCl$_3$, in the presence of phenyl hydrazine) δ 1.12 (d, 3H, *J* = 6.5 Hz), 0.90 (s, 9H), 0.55 (d, 3H, *J* = 6.8 Hz).

**2,2,5,5-Tetramethyl-4-(4-trifluoromethylphenyl0-3-azahexane 3-nitroxide (54).** The nitroxide, **54**, was prepared from *N-tert*-butyl-α-*tert*-butylnitrone, **52**, and 4-trifluoromethylphenylmagnesium bromide as described above and isolated as an orange solid (29% yield) TLC 16:1 hexane/ethyl acetate, molybdenum stain, $R_f$ = 0.52; mp 86−87 °C; IR(CDCl$_3$) 2974, 1617, 1326, 168, 1130, 1069 cm$^{-1}$; ESR (CH$_2$Cl$_2$) doubled triplet, $a_n$ = 15.021 G, $a_h$ = 2.198 G; MS (FAB) *m/z* 304 ([M + 1]$^+$, 62), 288 (68), 246 (76), 154 (100), 136 (69); HRMS exact mass calcd for [M + 2]$^+$ C$_{16}$H$_{25}$F$_3$NO 304.1890, found 304.1886; $^1$H NMR (250 MHz, CDCl$_3$, in the presence of phenyl hydrazine) δ 3.65 (s, 1H), 0.96 (s, 9H), 0.93 (s, 9H).

**2,3-Di-*tert*-butyl-4,5,6,7-tetrafluoro-1,2-benzisoxazolidine (20).** To a stirred suspension of magnesium turnings (101 mg, 4.20 mmol) and 3 mL of THF under nitrogen were added 200 mL of bromopentafluorobenzene. After 5 min, the rest of the bromopentafluorobenzene (300 mL, for a combined total of 500 mL, 4.00 mmol) was added over 10 min. The mixture was then stirred 1.5 h until most of the magnesium had disappeared. To this freshly prepared Grignard solution was added a solution of *N-tert*-butyl-α-*tert*-butylnitrone, **52** (315 mg, 2.00 mmol), in 3 mL of THF, and the light-brown homogeneous solution was stirred at room-temperature overnight. The excess Grignard reagent was decomposed by the addition of 10 mL of concentrated ammonium chloride solution and then 5 mL of water; all solids dissolved. The organic layer was separated, and the aqueous layer was extracted with 10 mL of diethyl ether. The organic layers were combined and concentrated, and to the residue was added 10 mL of methanol (some precipitate formed), 0.5 mL of concentrated NH$_4$OH, and 20.0 mg (0.10 mmol) of Cu(OAc)$_2$. A stream of air was bubbled through the yellow solution; no change of color was observed over a 1-h period. The mixture was left to stir overnight in an open flask and was concentrated, and the residue was dissolved in the mixture of 20 mL of chloroform, 5 mL of concentrated NaHSO$_4$ solution, and 20 mL of water. The organic layer was washed with 6 mL of saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered, and concentrated in vacuo to give the isoxazolidine, **20**, as a colorless solid (374 mg, 61% yield); TLC pure hexanes, molybdenum stain, $R_f$ = 0.58; $^1$H NMR (250 MHz, CDCl$_3$) δ 4.32 (s, 1H), 1.06 (s, 9H), 0.93 (s, 9H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) δ 143.0−111.9 (many peaks due to C−F coupling), 70.3 (d), 61.6 (s), 36.8 (s), 26.1 (q), 25.6 (q); ESMS *m/e* 306.10.

**2,2,5,5-Tetramethyl-4-diethylphosphono-3-azahexane 3-nitroxide (3).** The *N-tert*-butyl-α-*tert*-butylimine (500 mg, 3.50 mmol) and diethyl phosphite (distilled under nitrogen, 480 mg, 3.50 mmol) were heated to 75 °C and monitored by $^1$H NMR aliquots. After 4 h, little imine starting material could be seen by NMR. The reaction mixture was cooled, and diluted with 10 mL of diethyl ether, and washed twice with 3 mL of saturated sodium bicarbonate solution. After the mixture was dried over magnesium sulfate, all volatiles were removed in vacuo to give 562 mg of crude **22** as an oil (56% yield). This oil was directly submitted to oxidation. The amine, **22** (547 mg, 1.96 mmol), was dissolved in 4.0 mL of dichloromethane and cooled to 0 °C. A solution of purified *m*-chloroperbenzoic acid (509 mg, 2.94 mmol) in 7.0 mL of dichloromethane was added dropwise by cannula. The reaction mixture quickly became yellow. It was allowed to warm to room temperature and stirred for 1.5 h with the addition of enough dichloromethane to dissolve the precipitated *m*-chlorobenzoic acid. Anhydrous sodium carbonate (312 mg, 2.94 mmol) was added, and the bright orange reaction mixture was shaken with 10 mL of saturated sodium bicarbonate solution until all of the solids dissolved. The organic layer was dried over magnesium sulfate and the solvent evaporated to provide an orange-yellow oil. Purification by flash column chromatography, eluting with 2:1 hexane/ethyl acetate, gave the nitroxide **3** (246 mg, 43% yield); TLC 2:1 hexane/ethyl acetate, molybdenum stain, $R_f$ = 0.45; $^1$H NMR (250 MHz, CDCl$_3$, in the presence of phenylhydrazine) δ 3.89 (d, 1H, J = 9.3 Hz), 3.72 (d, 1H, J = 9.3 Hz), 2.50 (br s), 1.75 (br s), 1.70−1.40 (m), 1.27−0.75 (m).

**N-(2-Hydroxy-1,1-dimethylethyl)-α-*iso*propylnitrone. Mixture of Linear Nitrone and Cyclic Oxazolidine Tautomers 8 and 9.** A solution of ammonium chloride (3.21 g, 60.0 mmol) in water (40 mL) was added to a solution of 2-methyl-2-nitropropanol-1, **7** (5.95 g, 50.0 mmol), in ethanol (120 mL). The combined solution was stirred and

cooled in an ice bath while Zn dust (13.0 g, 200.0 mmol) was added in small portions over 15 min, and the resulting mixture was stirred for 4 h at room temperature under nitrogen. The mixture was filtered through a glass filter, and the cake was washed with hot 95% ethanol (70 mL) and hot chloroform (70 mL). The combined organic layers were evaporated, and the resulting clear oil was redissolved in chloroform (50 mL), dried over potassium carbonate, and filtered. To the chloroform solution of 2-hydroxyamino-2-methylpropan-1-ol was added isobutyraldehyde (5.44 mL, 60.0 mmol) and dried sodium carbonate, and the reaction mixture stirred at room temperature for 24 h. Purification by flash column chromatography, eluting with 5:1 ethyl acetate/methanol, afforded the desired nitrone as a 3:2 mixture of nitrone and cyclic oxazolidine tautomers, **8** and **9** (6.43 g, 82% yield); TLC 5:1 ethyl acetate/methanol, molybdenum stain, $R_f$ = 0.61; $^1$H NMR (250 MHz, CDCl$_3$, both tautomers) δ 7.2−6.8 (br s, 1H, cyclic form), 6.72 (d, 1H, J = 7.3 Hz, nitrone), 5.34 (br s, 1H, nitrone), 4.21 (d, 1H, J = 7.0 Hz, cyclic form), 3.73 (s, 2H, nitrone), 3.62 (q, 2H, J = 7.8 Hz, cyclic form), 3.3−3.1 (m, 1H, nitrone), 1.45 (s, 6H, nitrone), 1.20 (s, 6H, cyclic form), 1.12 (d, 6H, J = 7.3 Hz, nitrone), 0.99 (d, 6H, J = 7.0 Hz, cyclic form), $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 144.7 (d), 144.4 (s), 101.8 (d), 71.8 (t), 68.3 (t), 26.0 (q), 23.4 (q), 18.8 (q). HRMS exact mass calcd for [M + 1]$^+$ C$_8$H$_{17}$NO$_2$ 159.1259, found 159.1261.

**1-Trimethylsilyloxy-2-methyl-2-nitropropane (11).** 2-Methyl-2-nitropropan-1-ol, **7**, (5.95 g, 50.0 mmol) and pyridine (4.03 mL, 50.0 mmol) were dissolved in 50 mL of diethyl ether. Trimethylchlorosilane (6.34 mL, 50.0 mmol) was added dropwise at room temperature and the reaction mixture stirred for 2 h under nitrogen. Filtration of the precipitated pyridinium hydrochloride, followed by removal of the solvent gave the crude trimethylsilyl ether, **11**, which was purified by distillation (bp, 80 °C, 5 mm Hg) (8.15 g, 85% yield), $^1$H NMR (250 MHz, CDCl$_3$) δ 3.83 (s, 2H), 1.55 (s, 6H), 0.09 (s, 9H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) δ 88.6 (s), 68.7 (t), 22.7 (q), −0.7 (q).

**N-(2-Trimethylsilyloxy-1,1-dimethylethyl)-α-*iso*propylnitrone (13).** A mixture of 1-trimethylsilyloxy-2-methyl-2-nitropropane, **11** (4.03 g, 21.0 mmol), isobutyraldehyde (3.8 mL, 42 mmol), ammonium chloride (1.23 g, 23.0 mmol), diethyl ether (15 mL), and water (40 mL) was cooled to 0 °C, and Zn powder (5.46 g, 8.40 mmol) was added in small portions over 1 h with stirring. The resulting mixture was stirred for 24 h at room temperature under nitrogen and filtered, and the precipitate was washed twice with 5 mL of methanol. The product was extracted with dichloromethane (4 × 20 mL), and the combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. The crude product was purified by flash chromatography eluting with ethyl acetate, to give the nitrone, **13**, as a colorless oil (6.24 g, 57% yield); TLC ethyl acetate, molybdenum stain, $R_f$ = 0.37, IR(CDCl$_3$) 2964, 1587, 1253, 1104, 874, 842 cm$^{-1}$, $^1$H NMR (250 MHz, CDCl$_3$, both tautomers) δ 6.51 (d, 1H, J = 7.0 Hz), 3.61 (s, 2H), 3.10 (m, 1H), 1.33 (s, 6H), 1.02 (d, 6H, J = 6.8 Hz), 0.01 (s, 9H), $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 142.2 (d), 71.8 (s), 67.3 (t), 26.0 (d), 22.8 (q), 19.0 (q), −0.7 (q). HRMS exact mass calcd for [M + 1]$^+$ C$_{11}$H$_{25}$NO$_2$Si 231.1655, found 231.1654.

**Preparation of N-(2-Trimethylsilyloxy-1,1-dimethylethyl)-α-*iso*propylnitrone (13) from 8 and 9.** The mixture of tautomers, **8** and **9** (477 mg, 3.00 mmol), and pyridine (0.363 mL, 4.5 mmol) was dissolved in 6 mL of diethyl ether. Trimethylchlorosilane (0.57 mL, 4.5 mmol) was added dropwise and the reaction mixture stirred at room temperature for 12 h. The precipitate was then filtered and washed with dichloromethane, and the filtrate was evaporated to dryness. The crude product was purified by flash chromatography, eluting with ethyl acetate, to give the nitrone, **13**, as a colorless oil (493 mg, 71% yield). Spectral characteristics were the same as those described above.

**1-Trimethylsilyloxy-2,2,5-trimethyl-4-phenyl-3-azahexane 3-nitroxide (12).** *N*-(2-Trimethylsilyloxy-1,1-dimethylethyl)-α-isopropylnitrone, **13** (8.34 g, 35.9 mmol), was dissolved under nitrogen in dry THF (50 mL) and cooled to 0 °C. A 3.0 M solution of phenylmagnesium bromide (23.9 mL, 71.8 mmol) in diethyl ether was added dropwise by cannula at this temperature over 10 min. During the addition the mixture turned dark, and some precipitate formed. After the mixture had been stirred at room temperature for 2 h, excess Grignard reagent was decomposed by the addition of concentrated

ammonium chloride (50 mL) and water (25 mL) until all of the solids dissolved. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (2 × 40 mL). The combined organic layers were then washed with brine (20 mL), and the residue was treated with a mixture of methanol (150 mL), concentrated NH$_4$OH (4 mL), and Cu(OAc)$_2$ (359 mg, 1.80 mmol) to give a brown solution. A stream of air was bubbled through the solution for 30 min during which time it turned dark green. This was concentrated and the residue partitioned between chloroform (50 mL) and 2 M NH$_4$OH (50 mL). The organic layer was separated, and the aqueous layer was extracted with chloroform (2 × 20 mL). The combined organic layers were then washed with 20 mL of brine (light emulsion), dried over magnesium sulfate, and concentrated in vacuo. The crude product was purified by flash chromatography eluting with 16:1 hexane/ethyl acetate to afford the nitroxide, **12**, as an orange oil (3.85 g, 35% yield); TLC 16:1 hexane/ ethyl acetate, molybdenum stain, $R_f = 0.53$, IR(CDCl$_3$) 2960, 1252, 1102, 874, 842 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, in the presence of phenyl hydrazine) $\delta$ 3.44 (d, 1H, $J_{gem}$ = 9.5 Hz), 3.32 (d, 1H, $J_{gem}$ = 9.5 Hz), 1.18 (d, 3H, $J$ = 6.5 Hz), 1.14 (s, 3H), 0.78 (s, 3H), 0.61 (d, 3H, $J$ = 6.8 Hz), 0.05 (s, 9H); HRMS exact mass calcd for [M + 1]$^+$ C$_{17}$H$_{30}$NO$_2$Si 308.2045, found 308.2049.

**N-iso-propyl-α-iso-propylnitrone (16).** A mixture of 2-nitropropane, **15** (445 mg, 5.0 mmol), isobutyraldehyde (453 mL, 5.0 mmol), ammonium chloride (294 mg, 5.5 mmol), and water (20 mL) was cooled to 0 °C in an ice-bath under ambient atmosphere. While stirring, Zn powder (1.30 g, 20.0 mol) was added over 30 s, and the resulting mixture was allowed to stir in the ice-bath and warm overnight. After that, the mixture was filtered through a glass filter and the cake washed twice with 2 mL of methanol. The product was extracted four times with 10 mL of dichloromethane. The combined organic layers were then dried over magnesium sulfate and concentrated in vacuo to give the nitrone, **16**, as a colorless low-melting solid (1.01 g, 78% yield); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.59 (d, 1H, $J$ = 7.3 Hz), 4.00 (hept, 1H, $J$ = 6.5 Hz), 3.18 (m, 1H), 1.41 (d, 6H, $J$ = 6.5 Hz), 0.60 (d, 6H, $J$ = 7.3 Hz); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) $\delta$ 141.8 (d), 65.8 (d), 25.4 (d), 20.5 (q), 18.7 (q).

**N-iso-Propyl-α-tert-butylnitrone (17).** The nitrone, **17**, was prepared from pivalaldehyde (900 mg, 10.5 mmol), 2-nitropropane, **15** (890 mg, 10.0 mmol), ammonium chloride (588 mg, 11.0 mmol), and Zn powder (2.60 g, 40.0 mol) in 20 mL of water as described above. The desired nitrone, **17**, was isolated as a colorless solid (70% yield); $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 6.52 (s, 1H), 3.98 (hept, 1H), 1.39 (d, 6H, $J$ = 6.5 Hz), 1.27 (s, 9H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) $\delta$ 142.0 (d), 66.8 (d), 32.5 (s), 26.1 (q), 20.8 (q).

**General Procedure for the Formation of Alkoxyamines using PbO$_2$. 2,2,5-Trimethyl-3-(1−phenylethoxy)-4-phenyl-3-azahexane (29).** A two-phase mixture of 1-bromoethylbenzene (11.1 g, 60.0 mmol) and fuming hydrazine (19.2 mL, 600 mmol) was solicited for 30 min under nitrogen until a single cloudy phase was observed. The mixture was diluted with 10 mL of diethyl ether, and the organic and hydrazine layers were separated. The hydrazine layer was washed with 500 mL of diethyl ether. The organic phases were combined and washed with 250 mL of 10% aqueous potassium hydroxide followed by 250 mL of brine, dried over magnesium sulfate, and filtered. Volatiles were removed in vacuo to give a slightly yellow oil which was diluted with toluene (50 mL) and cooled to −78 °C. In a separate flask, lead dioxide (21.5 g, 90 mmol), 2,2,5-trimethyl-4-phenyl-3-azahexane 3-nitroxide, **1** (6.61 g, 30 mmol), and toluene (50 mL) were sonicated under nitrogen for 5 min and then cooled to −78 °C. The benzylic hydrazine solution was added by cannula, and the residues were washed in with an additional 25 mL of toluene. The reaction mixture was allowed to warm to room temperature over 1 h, diluted with 500 mL of diethyl ether, filtered through Celite, and washed with 250 mL of diethyl ether. Volatiles were removed in vacuo to give a colorless oil. Purification by flash column chromatography (100:1 hexane/ethyl acetate) afforded 7.10 g of alkoxyamine, **29**, as a colorless oil (73% yield). The coupling product was determined to be a 1:1.3 mixture of the diastereomers as indicated by integration of the methyl hydrogens at $\delta$ 0.54 and 0.22 ppm. TLC 100:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.48$; IR(CDCl$_3$) 2956, 1492, 1452, 1382, 1207, 1061 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) $\delta$ 7.5−7.1 (m, 20H), 4.90 (q + q,

2H, $J$ = 6.5 Hz, both diastereomers), 3.41 (d, 1H, $J$ = 10.8 Hz, major diastereomer), 3.29 (d, 1H, $J$ = 10.8 Hz, minor diastereomer), 2.35 (two m, 2H, both diastereomers), 1.62 (d, 3H, $J$ = 6.8 Hz, major diastereomer), 1.54 (d, 3H, $J$ = 7.0 Hz, minor diastereomer), 1.31 (d, 3H, $J$ = 6.3 Hz, major diastereomer), 1.04 (s, 9H, minor diastereomer), 0.92 (d, 3H, minor diastereomer), 0.77 (s, 9H, major diastereomer), 0.54 (d, 3H, $J$ = 6.5 Hz, major diastereomer), 0.22 (d, 3H, $J$ = 6.5 Hz, minor diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) $\delta$ 145.87 (s), 145.08 (s), 142.56 (s), 142.35 (s), 131.03 (d), 128.15 (d), 127.46 (d), 127.37 (d), 127.28 (d), 127.09 (d), 126.70 (d), 126.43 (d), 126.25 (d), 83.58 (d), 82.91 (d), 72.30 (d), 72.21 (d), 60.59 (s), 60.45 (s), 32.12 (d), 31.69 (d), 28.48 (q), 28.3 (q), 24.81 (q), 23.26 (q), 23.23 (q), 22.05 (q), 21.26 (q), 21.14 (q). MS (FAB) *m/z* 326 ([M + 1]$^+$, 3), 221 (11), 178 (31), 148 (15), 133 (75), 122 (21), 106 (17), 105 ([C$_8$H$_9$]$^+$, 100); HRMS exact mass calcd for [M + 1]$^+$ C$_{22}$H$_{32}$NO 326.2484, found 326.2485.

**1-(trans-2,5-Dimethyl-2,5-diphenylpyrrolidine-1-oxy)-1-phenyl- ethane (26).** The alkoxyamine, **26**, was prepared from the $C_2$-symmetric nitroxide *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-1-oxyl, **55**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with 95:5 hexane/ethyl acetate, gave the desired alkoxyamine, **26**, as a colorless oil (62% yield). The major and minor diastereomers were obtained as an inseparable mixture in a 2.5:1 ratio as elucidated by integration of the 500 MHz $^1$H NMR spectrum; TLC 95:5 hexane/ethyl acetate, UV, *p*-anisaldehyde stain, $R_f = 0.3$; IR(CDCl$_3$) 2966, 1461, 1379, 1261, 1091, 1014 cm$^{-1}$; $^1$H NMR (500 MHz, CD$_3$OD, major and minor diastereomers) $\delta$ 6.96− 7.69 (m, 30H), 4.22 (major, q, 1H, $J$ = 6.5), 4.23 (minor, q, 1H, $J$ = 6.5), 2.46−2.66 (m, 2H), 2.12−2.22 (m, 2H), 1.86−2.04 (m, 4H), 1.57 (minor, s, 3H), 1.22 (major, s, 3H), 1.20 (minor, d, 3H, $J$ = 6.5), 1.04 (major, s, 3H), 1.03 (minor, s, 3H), 1.00 (major, d, 3H, $J$ = 6.5); $^{13}$C NMR (125 MHz, CD$_3$OD, major and minor diastereomers) $\delta$ 153.61 (s), 153.36 (s), 145.71 (s), 145.71 (s), 145.05 (s), 144.84 (s), 129.78 (d), 129.04 (d), 128.97 (d), 128.81 (d), 128.54 (d), 128.44 (d), 128.11 (d), 127.80 (d), 127.69 (d), 127.48 (d), 127.32 (d), 126.94 (d), 82.73 (major, d), 81.88 (minor, d), 70.80 (major, s), 69.75 (major, s), 69.75 (minor, s), 68.9 (major, s) 41.63(major, t), 41.48 (minor, t), 34.95 (minor, t), 34.71 (major, t), 30.51 (major, q), 30.51 (minor, q), 25.02 (minor, q), 23.61 (major, q), 22.43 (minor, q), 22.26 (major, q); LRMS *m/z* 372 [M + H]$^+$, 356, 267, 252, 190, 118, 105; HRMS Calcd for C$_{26}$H$_{29}$NO 372.2327 [M + H], found 372.2325.

**2,2,5,5-Tetramethyl-3-(1−phenylethoxy)-4-diethylphosphono-3- azahexane (27).** The alkoxyamine, **27**, was prepared from 2,2,5,5- tetramethyl-4-diethylphosphono-3-azahexane-3-nitroxide, **3**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography (2:1 pentane/diethyl ether) afforded **27** as a colorless oil, 34% yield that was determined to be a 1:1.6 mixture of the diastereomers by integration of the methine hydrogens at $\delta$ 5.24 and 4.99 ppm, respectively. In this case the diastereomers were separated by flash chromatography fraction I: TLC 1:1 pentane/diethyl ether, molybdenum stain, $R_f = 0.57$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.5−7.2 (m, 5H), 5.24 (q, 1H, $J$ = 6.5 Hz), 4.05−3.75 (m, 2H), 3.41 (d, 1H, $J$ = 26.0 Hz), 3.50−3.30 (m, 2H), 1.56 (d, 3H, $J$ = 6.5 Hz), 1.3−1.1 (m, 21H), 0.88 (t, 3H, $J$ = 7.0 Hz); fraction II TLC 1:1 pentane/ diethyl ether, molybdenum stain, $R_f = 0.44$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.5−7.2 (m, 5H), 4.99 (q, 1H, $J$ = 6.5 Hz), 4.5−3.9 (m, 4H), 3.35 (d, 1H, $J$ = 26.0 Hz), 1.60 (d, 3H, $J$ = 6.5 Hz), 1.4−1.2 (m, 15H), 0.84 (s, 9H).

**cis-1,3-Dimethyl-2-(1−phenylethoxy)-1,3-diphenylisoindoline (30a).** The alkoxyamine, **30a**, was prepared from *meso*-1,3-dimethyl-1,3- diphenylisoindolin-2-yloxyl, **56**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with 50:1 to 16:1 hexane/ethyl acetate, afforded **30a** as a colorless oil, (32% yield). TLC 32:1 hexane/ethyl acetate, molybdenum stain, $R_f = 0.30$; IR(CDCl$_3$) 3025, 2990, 1602, 1496, 1449, 1301, 1067 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) $\delta$ 7.60 (d, 2H, $J$ = 7.3 Hz), 7.5−6.7 (m, 17H), 4.12 (q, 1H, $J$ = 6.5 Hz), 1.99 (s, 3H), 1.86 (s, 3H), 0.84 (d, 3H, $J$ = 6.5 Hz); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) $\delta$ 148.29 (s), 147.99 (s), 146.35 (s), 145.87 (s), 143.68 (d), 128.16 (d), 127.8 (d), 127.73 (d), 127.6 (d), 127.53 (d), 126.92 (d), 126.76 (d), 126.49 (d), 126.37 (d), 123.3 (d), 80.85 (d), 73.11 (s), 72.88 (s), 22.75 (q), 22.59 (q), 21.78

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(q). MS (FAB) *m/e* 420 ([M$^+$ + 1], 18), 315 ([nitroxide$^+$ + 1], 88), 300 ([nitroxide$^+$ − CH$_2$], 100), 104 ([styrene$^+$], 79); HRMS exact mass calcd for [M$^+$ + 1] C$_{30}$H$_{30}$NO 420.23274, found 420.2328.

***trans*-1,3-Dimethyl-2-(1-phenylethoxy)-1,3-diphenylisoindoline (30b).** The alkoxyamine, **35**, was prepared from *d,l*-1,3-dimethyl-1,3-diphenylisoindoline 2-nitroxide, **57**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with 5:1 hexane/dichloromethane, afforded **30b** as a colorless oil, 81% yield which was determined to be a 2.2:1 mixture of diastereomers (as indicated by integration of the methyl hydrogens at δ 2.16 and 1.73 ppm); TLC 5:1 hexane/dichloromethane, molybdenum stain, $R_f$ = 0.28; IR(CDCl$_3$) 3061, 3032, 2977, 2931, 1600, 1493, 1448, 1370, 1070 cm$^{-1}$; $^1$H NMR (500 MHz, C$_6$D$_6$, both diastereomers) δ 7.8−6.6 (m, 19H), 4.51−4.44 (q + q, 1H, both diastereomers), 2.16 (s, 3H, minor diastereomer), 1.73 (s, 3H, major diastereomer), 1.62 (s, 3H, major diastereomer), 1.57 (s, 3H, minor diastereomer), 1.54 (d, 3H, *J* = 6.5 Hz, minor diastereomer), 1.12 (d, 3H, *J* = 7.0 Hz, major diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 148.7 (s), 147.6 (s), 144.0 (s), 143.6 (s), 143.2 (s), 129.9 (d), 129.7 (d), 128.2 (d), 128.1 (d), 128.0 (d), 127.9 (d), 127.73 (d), 127.65 (d), 127.5 (d), 127.4 (d), 127.0 (d), 126.9 (d), 126.82 (d), 126.76 (d), 126.5 (d), 126.3 (d), 123.5 (d), 123.3 (d), 121.6 (d), 81.7 (d), 80.4 (d), 72.5 (s), 72.2 (s), 29.1 (q), 28.3 (q), 22.7 (q), 22.5 (q), 21.1 (q), 20.1 (q). MS (FAB) *m/e* 420 ([M$^+$ + 1], 15), 315 ([nitroxide$^+$ + 1], 100), 300 ([nitroxide$^+$ − CH$_2$], 77), 104 ([styrene]$^+$, 63); HRMS exact mass calcd for [M$^+$ + 1] C$_{30}$H$_{30}$NO 420.2327, found 420.2328.

**2,2,5,5-Tetramethyl-3-(1−phenylethoxy)-4-phenyl-3-azahexane (31).** The alkoxyamine, **31**, was prepared from 2,2,5,5-tetramethyl-4-phenyl-3-azahexane-3-nitroxide, **52** (70.3 mg, 0.30 mmol), using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with pure hexanes, afforded **31** as a colorless oil, 59% yield which was determined to be a 1:1.3 mixture of the diastereomers by integration of the methine hydrogens at δ 5.25 and 5.10 ppm; TLC hexanes, molybdenum stain, $R_f$ = 0.27; IR(CDCl$_3$) 2973, 1481, 1451, 1362, 1198, 1059 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.6−7.0 (m, 20H), 5.25 (q, 1H, *J* = 6.5 Hz, minor diastereomer), 5.10 (q, 1H, *J* = 6.8 Hz, major diastereomer), 3.85 (s, 1H, minor diastereomer), 3.76 (s, 1H, major diastereomer), 1.67 (d, 3H, *J* = 6.8 Hz, major diastereomer), 1.62 (d, 3H, *J* = 6.5 Hz, minor diastereomer), 1.09 (s, 9H, minor diastereomer), 1.07 (s, 9H, major diastereomer), 0.93 (s, 9H, minor diastereomer), 0.72 (s, 9H, major diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 145.59 (s), 144.20 (s), 140.35 (s), 139.63 (s), 132.95 (d), 128.22 (d), 128.07 (d), 127.85 (d), 127.64 (d), 127.21 (d), 127.03 (d), 126.76 (d), 126.55 (d), 126.47 (d), 126.16 (d), 126.03 (d), 82.65 (d), 77.91 (d), 74.27 (d), 74.12 (d), 61.65 (s), 61.41 (s), 35.67 (s), 35.48 (s), 29.42 (q), 29.28 (q), 29.0 (q), 24.14 (q), 22.90 (s). MS (FAB) *m/z* 340 ([M+1]$^+$, 1), 234 ([nitroxide]$^+$, 38), 179 (14), 178 ([nitroxide-C$_4$H$_8$]$^+$, 100), 147 (32), 122 (18), 105 ([C$_8$H$_9$]$^+$, 56); HRMS exact mass calcd for [M+1]$^+$ C$_{23}$H$_{34}$NO 340.2640, found 340.2640.

**3,3′-Dimethyl-N-(1′-phenylethoxy)-1-oxa-4-aza-spiro[4,5]-decane (32).** The alkoxyamine, **32**, was prepared from 3,3′-dimethyl-*N*-(oxyl)-1-oxa-4-azaspiro[4,5]decane, **58**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with 16:1 hexane/ethyl acetate, afforded **35** as a colorless oil, (33%, yield); IR (CDCl$_3$) 3036, 2931, 2247, 1598, 1486, 1446, 1262, 1210, 1059, 927, 894, 697 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 7.32−7.34 (m, 5H), 4.61 (q, 1H, *J* = 6.6 Hz), 3.4−3.6 (m, 2H), 1.0−2.0 (m, 6H), 1.48 (d, 3H, *J* = 6.6 Hz), 1.28 (s, 1.5H), 1.26 (s, 1.5H), 1.07 (s, 1.5H), 0.71 (s, 1.5H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) δ 143.8 (4°), 128.6 (d), 128.1 (d), 127.5 (d), 127.4 (d), 99.5 (4°), 99.0 (4°), 82.1 (d), 74.2 (t), 73.7 (t), 63.8 (4°), 63.4 (4°), 38.0 (t), 37.3 (t), 32.8 (t), 32.7 (t), 27.2 (q), 27.0 (q), 25.7 (t), 25.4 (t), 24.0 (t), 23.9 (t), 23.2 (t), 23.1 (t), 21.9 (q), 21.4 (q); Anal. Calcd for C$_{18}$H$_{27}$NO$_2$ C, 74.7; H, 9.4; N, 4.8. Found C, 74.56; H, 9.28, N, 4.75.

**1-Hydroxy-2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (33).** To a solution of 1-trimethylsilyloxy-2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane, **35** (100 mg, 0.241 mmol), in methanol (5 mL) was added citric acid (50 mg), and the reaction was stirred at room temperature for 5 min. The solution was concentrated in vacuo and the crude product purified by flash chromatography,

eluting with hexane/ethyl acetate 30:1 to give the hydroxy-functionalized alkoxyamine, **33**, as a colorless oil (77 mg, 93% yield); TLC hexane/ethyl acetate 4:1, molybdenum stain, $R_f$ = 0.25, IR(CDCl$_3$) 3063, 2978, 1452, 1366, 1058 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.5−7.1 (m, 20H), 5.0−4.8 (m, 2H), 3.7−2.2 (m, 9H), 1.65 (d, 3H, *J* = 6.8 Hz), 1.56 (d, 3H, *J* = 6.8 Hz), 1.5−1.4 (m, 1H), 1.35 (d, 3H, *J* = 6.3 Hz), 1.27 (s, 3H), 1.11 (s, 3H), 0.86 (s, 3H), 0.85 (d, 3H, *J* = 6.3 Hz), 0.68 (s, 3H), 0.58 (d, 3H, *J* = 6.8 Hz), 0.41 (s, 3H), 0.22 (d, 3H, *J* = 6.5 Hz); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 144.5 (s), 144.2 (s), 141.5 (s), 141.2 (s), 130.6 (d), 130.6 (d), 128.4 (d), 128.3 (d), 127.7 (d), 127.5 (d), 127.5 (d), 127.0 (d), 126.9 (d), 126.7 (d), 126.1 (d), 83.4 (d), 83.4 (d), 72.5 (d), 72.1 (d), 70.1 (t), 69.6 (t), 63.7 (s), 63.3 (s), 31.9 (d), 31.2 (d), 25.4 (q), 25.0 (q), 24.4 (q), 23.2 (q), 22.1 (q), 22.1 (q), 21.2 (q), 20.9 (q), 20.1 (q), 19.4 (q); HRMS exact mass calcd for [M + 1]$^+$ C$_{22}$H$_{31}$NO$_2$ 341.2354, found 341.2355.

**Methyl 2-(*trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-1-oxy) propionate (34).** A solution of methyl propionate (43 μl, 0.450 mmol) in 1.6 mL of THF was cooled to −78 °C, and 2 M LDA in heptane/THF/ethylbenzene (300 μl, 0.600 mmol) was added. The mixture was stirred at −78 °C for 3 h and added dropwise to a mixture of the $C_2$ symmetric nitroxide *trans*-2,5-dimethyl-2,5-diphenylpyrrolidine-1-oxyl (79.9 mg, 0.300 mmol) and CuCl$_2$ (anhyd, 64.5 mg, 0.480 mmol) in THF (1.5 mL), cooled to −78 °C. The reaction mixture was allowed to warm to room temperature overnight, diluted with ether (20 mL), and washed with saturated NaHSO$_4$ (10 mL) and saturated NaCl (10 mL). The ether layer was dried over magnesium sulfate and filtered, and the volatiles were removed in vacuo to give a yellow oil, which was purified by flash column chromatography, eluting with 93:7 hexane/ethyl acetate, to give the alkoxyamine, **34**, as a pale yellow oil (58 mg, 55% yield). The major and minor diastereomers were obtained as an inseparable mixture in a 1.1:1 ratio as elucidated by integration of the 500 MHz $^1$H NMR spectrum in CDCl$_3$; TLC 93:7 hexane/ethyl acetate, UV, *p*-anisaldehyde stain, $R_f$ = 0.44; IR(CDCl$_3$) 2978, 1743, 1490, 1449, 1373, 1279, 1208, 1091 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$, major and minor diastereomers) δ 7.18−7.77 (m, 20H), 4.22 (minor, q, 1H, *J* = 7.5), 3.97 (major, q, 1H, *J* = 7), 3.73 (major, s, 3H), 3.15 (minor, s, 3H), 2.52−2.62 (m, 2H), 2.14−2.30 (m, 2H), 1.90−2.06 (m, 4H), 1.60 (s, 3H), 1.59 (s, 3H), 1.37 (s, 3H), 1.15 (s, 3H), 1.14 (minor, d, 3H, *J* = 7.5), 0.97 (d, 3H, *J* = 7); $^{13}$C NMR (125 MHz, CDCl$_3$, major and minor diastereomers) δ 174.00 (major, s), 173.76 (minor, s), 151.60 (s), 151.52 (s), 142.93 (major, s), 142.93 (minor, s), 128.47 (d), 128.25 (d), 128.05 (d), 127.83 (d), 127.60 (d), 127.52 (d), 126.68 (d), 126.54 (d), 126.15 (d), 125.95 (d), 125.81 (d), 125.75 (d), 125.56 (d), 125.40 (d), 80.56 (minor, d), 79.25 (major, d), 69.95 (minor, s), 68.49 (minor, s), 68.32 (minor, s), 67.26 (major, s), 51.44 (q), 51.05 (minor, q), 40.35 (minor, t), 40.21 (major, t), 33.17 (minor, t), 32.83 (major, t), 29.90 (major, q), 29.51 (minor, q), 23.99 (minor, q), 22.58 (major, q), 17.52 (major, q), 17.38 (minor, q); LRMS *m/z* 354 [M + H]$^+$, 338, 266, 250, 236, 222, 157, 131, 118; HRMS Calcd for C$_{22}$H$_{27}$NO$_3$ 353.1990 [M], found 353.1990.

**1-Trimethylsilyloxy-2,2,5-trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (35).** The alkoxyamine, **35**, was prepared from 1-trimethylsilyloxy-2,2,5-tetramethyl-4-phenyl-3-azahexane-3-nitroxide, **12**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography, eluting with hexane/ethyl acetate 30:1, afforded **35** as a colorless oil, 66% yield which was determined to be a 1:1 mixture of diastereomers; TLC hexane/ethyl acetate, 30:1, molybdenum stain, $R_f$ = 0.43; IR(CDCl$_3$) 2957, 1251, 1092, 1060 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.6−7.1 (m, 20H), 5.0−4.8 (m, 2H), 3.6−3.3 (m, 2H), 3.0−2.9 (m, 2H), 2.4−2.3 (m, 1H), 1.62 (d, 3H, *J* = 6.8 Hz), 1.53 (d, 3H, *J* = 6.8 Hz), 1.4−1.3 (m, 1H), 1.31 (d, 3H, *J* = 6.5 Hz), 1.09 (s, 3H), 0.93 (s, 3H + d, 2H), 0.86 (s, 3H), 0.54 (s, 3H + d, 2H), 0.20 (d, 3H, *J* = 6.8 Hz), 0.08 (s, 9H), −0.16 (s, 9H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 145.7 (s), 145.0 (s), 142.7 (s), 132.4 (s), 130.9 (d), 128.3 (d), 128.1 (d), 127.9 (d), 127.5 (d), 127.4 (d), 127.3 (d), 127.0 (d), 126.9 (d), 126.5 (d), 126.2 (d), 83.6 (d), 82.7 (d), 72.1 (d), 72.0 (d), 69.5 (t), 69.2 (t), 64.4 (s), 64.3 (s), 32.0 (d), 31.6 (d), 24.8 (q), 23.5 (q), 23.2 (q), 23.2 (q), 22.1 (q), 21.9 (q), 21.7 (q), 21.3 (q), 21.2 (q), 20.4 (q), −0.4

(q), −0.6 (q); HRMS exact mass calcd for [M + 1]$^+$ C$_{25}$H$_{39}$NO$_2$Si 413.2749, found 413.2747.

**2,2,5,5-Tetramethyl-3-(1-phenylethoxy-4-(4-trifluoromethylphenyl)-3-azahexane (36).** The alkoxyamine, **36**, was prepared from 2,2,5,5-tetramethyl-4-(4-trifluoromethylphenyl)-3-azahexane-3-nitroxide, **54**, using the general PbO$_2$ procedure as described above. Purification by flash column chromatography (pure hexanes) afforded **36** as a colorless oil, 88% yield which was determined to be a 1:1.8 mixture of the diastereomers by integration of the methine hydrogens at δ 5.25 and 5.14 ppm; TLC pure hexanes, molybdenum stain, $R_f$ = 0.49; $^1$H NMR (500 MHz, CDCl$_3$, both diastereomers) δ 7.8−7.2 (m, 18H), 5.25 (q, 1H, *J* = 6.8 Hz, minor diastereomer), 5.14 (q, 1H, *J* = 7.0 Hz, major diastereomer), 3.94 (s, 3H, minor diastereomer), 3.86 (s, 3H, major diastereomer), 1.71 (d, 3H, *J* = 7.0 Hz, major diastereomer), 1.65 (d, 3H, *J* = 6.8 Hz, minor diastereomer), 1.12 (s, 3H, minor diastereomer), 1.10 (s, 3H, major diastereomer), 0.95 (s, 3H, minor diastereomer), 0.76 (s, 3H, major diastereomer); $^{13}$C NMR (APT) (125 MHz, CDCl$_3$, both diastereomers) δ 145.3 (s), 145.08 (s), 143.9 (s), 133.2 (d), 132.5 (d), 128.5 (d), 128.2 (d), 127.4 (d), 127.2 (d), 126.5 (d), 123.7 (d), 123.5 (d), 83.0 (d), 78.6 (d), 73.9 (d), 73.8 (d), 61.9 (s), 61.7 (s), 35.8 (s), 35.6 (s), 29.3 (q), 29.2 (q), 29.1 (q), 29.0 (q), 24.0 (q), 23.1 (q). MS (FAB) *m/z* 408 ([M + 1]$^+$, 26), 302 ([nitroxide]$^+$, 57), 286 (51), 246 (64); HRMS exact mass calcd for [M + 1]$^+$ C$_{24}$H$_{33}$F$_3$NO 408.2515, found 408.2509.

**2,2,5-Trimethyl-3-(1-phenylethoxy)-4-(4-trifluoromethylphenyl)-3-azahexane (37).** The alkoxyamine, **37**, was prepared from 2,2,5-trimethyl-4-(4-trifluoromethylphenyl)-3-azahexane-3-nitroxide, **53** (70.3 mg, 0.30 mmol), using the general PbO$_2$ procedure as described above. Purification by flash column chromatography (pure hexanes) afforded **37** as a colorless oil, 58% yield which was determined to be a 1:1.1 mixture of the diastereomers by integration of the methyl hydrogens at δ 1.04 and 0.77 ppm; TLC pure hexanes, molybdenum stain, $R_f$ = 0.44; IR (CDCl$_3$) 2976, 1617, 1363, 1326, 1166, 1127, 1068 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.7−7.2 (m, 18H), 5.0−4.8 (m, 1H), 3.49 (d, 1H, *J* = 10.5 Hz, major diastereomer), 3.36 (d, 1H, *J* = 11.0 Hz, minor diastereomer), 1.63 (d, 3H, *J* = 6.8 Hz, minor diastereomer), 1.55 (d, 3H, *J* = 6.8 Hz, major diastereomer), 1.32 (d, 3H, *J* = 6.3 Hz, major diastereomer), 1.04 (s, 9H, minor diastereomer), 0.93 (d, 3H, *J* = 6.3 Hz, minor diastereomer), 0.77 (s, 9H, major diastereomer), 0.53 (d, 3H, *J* = 6.5 Hz, major diastereomer), 0.19 (d, 3H, *J* = 6.5 Hz, minor diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 145.9 (s), 146.6 (s), 145.5 (s), 144.7 (s), 131.2 (d), 128.4 (d), 128.3 (d), 127.6 (d), 127.1 (d), 126.9 (d), 126.2 (d), 124.3 (d), 124.2 (d), 124.1 (d), 83.8 (d), 83.2 (d), 71.8 (d), 71.7 (d), 60.7 (s), 60.6 (s), 32.1 (d), 31.6 (d), 28.5 (q), 28.3 (q), 24.7 (q), 23.1 (q), 22.1 (q), 22.0 (q), 21.1 (q), 20.9 (q). MS (FAB) *m/z* 394 ([M + 1]$^+$, 1.7), 302 ([nitroxide]$^+$, 57), 246 (18), 201 (23), 159 (24), 105 (100); HRMS exact mass calcd for [M + 1]$^+$ C$_{23}$H$_{31}$F$_3$NO 394.2357, found 394.2356.

**General Procedure for Alkoxyamine Formation by Manganese Coupling. 2,2,5-Trimethyl-3-(1-(4′-chloromethyl)phenylethoxy)-4-phenyl-3-azahexane (43).** To a solution of p-vinyl benzyl chloride (6.10 g, 40.0 mmol) and 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide, **1** (4.40 g, 20.0 mmol), in 1:1 toluene/ethanol (150 mL) was added [*N,N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminato] manganese(III) chloride (2.80 g, 4.0 mmol) followed by di-*tert*-butyl peroxide (4.30 g, 30.0 mmol) and sodium borohydride (2.28 g, 60.0 mmol). The reaction mixture was then stirred at room temperature for 12 h, evaporated to dryness, and partitioned between dichloromethane (150 mL) and water (200 mL). The aqueous layer was further extracted with dichloromethane (3 × 100 mL). The combined organic layers were then dried and evaporated to dryness, and the crude product was purified by flash chromatography, eluting with 1:9 hexane gradually increasing to 1:3 dichloromethane/hexane. The desired chloromethyl alkoxyamine, **43**, was obtained as a colorless oil, (4.03 g, 62% yield); IR(CDCl$_3$) 2950, 1490, 1450, 1390, 1210, 1065 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.4−7.1 (m, 18H), 4.95 (q + q, 2H, *J* = 6.5 Hz, both diastereomers), 4.67 and 4.63 (each s, 4H, CH$_2$Cl), 3.49 (d, 1H, *J* = 10.8 Hz, major diastereomer), 3.36 (d, 1H, *J* = 10.8 Hz, minor diastereomer), 2.38 (two m, 2H, both diastereomers), 1.66 (d, 3H, *J* = 6.8 Hz, major diastereomer), 1.34 (d, 3H, *J* = 7.0 Hz, minor

diastereomer), 1.08 (s, 9H, minor diastereomer), 0.95 (m, 3H, minor diastereomer), 0.79 (s, 9H, major diastereomer), 0.61 (d, 3H, *J* = 6.5 Hz, major diastereomer) and 0.30 (d, 3H, *J* = 6.5 Hz, minor diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 146.10 (s), 145.18 (s), 142.61 (s), 142.33 (s), 135.73 (d), 130.97 (d), 128.40 (d), 127.37 (d), 127.32 (d), 127.21 (d), 127.00 (d), 126.49 (d), 126.37 (d), 126.21 (d), 83.17 (d), 82.25 (d), 72.17 (d), 72.14 (d), 60.49 (s), 60.45 (s), 46.23 (t), 32.02 (d), 31.72 (d), 28.39 (q), 28.22 (q), 24.68 (q), 23.10 (q), 23.03 (q), 22.09 (q), 21.33 (q), 21.12 (q); Anal. Calcd for C$_{23}$H$_{32}$ClNO C, 73.9; H, 8.62; N, 3.75. Found C, 74.1; H, 8.84; N, 3.77.

**4,4-Dimethyl-2,2-dipentyl-N-(1′-phenylethoxy)-1-oxa-3-azacyclopentane (39).** The alkoxyamine, **39**, was prepared from 4,4-dimethyl-2,2-dipentyl-*N*-(oxyl)-1-oxa-3-azacyclopentane, **60**, using the general manganese procedure as described above. Purification by flash column chromatography, eluting with 1:3 dichloromethane/hexane, afforded **39** as a colorless oil, (60% yield); IR (CDCl$_3$) 2950, 1600, 1490, 1210, 1065, and 710 cm$^{-1}$; $^1$H NMR (250 MHz, CDCl$_3$) δ 7.30−7.40 (m, 5H), 4.60 (q, 1H, *J* = 6.6 Hz), 3.4−3.6 (m, 2H), and 1.0−2.0 (m, 31H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$) δ 144.51, 128.65, 128.12, 127.63, 127.41, 99.33, 83.03, 74.15, 63.48, 38.03, 37.94, 27.24, 27.08, 26.88, 25.95, 25.49, 23.67, 23.40, 21.9, 20.58, 19.62, and 19.06; Anal. Calcd for C$_{23}$H$_{39}$NO$_2$ C, 76.4; H, 10.87; N, 3.87. Found C, 76.2; H, 10.93, N, 4.01.

**1-(3-cyano-2,2,5,5-tetramethylpyrrolidine-1-oxy)-1-phenylethane (40).** The alkoxyamine, **40**, was prepared from the 3-cyano-2,2,5,5-tetramethylpyrrolidine-1-oxyl, **59**, using the general manganese procedure as described above. Purification by flash column chromatography, eluting with 1:3 dichloromethane/hexane, gradually increasing to 3:1 dichloromethane/hexane, gave the desired alkoxyamine, **40**, as a colorless oil (71% yield); $^1$H NMR (500 MHz, CDCl$_3$) δ 7.25−7.40 (m, 5H), 4.44 (q, 1H, *J* = 6.5), 3.23 (q, 1H), 1.80−2.10 (m, 2H), 1.55 (d, 3H), 0.75, 0.91, 1.04, and 1.22 (each s, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.60, 129.81, 128.85, 128.45, 128.32, 127.80, 126.90, 82.54, 41.14, 30.50, 29.63, 25.00, 23.65, 22.89, and 22.20; Anal. Calcd for C$_{17}$H$_{24}$N$_2$O C, 79.02; H, 9.36; N, 10.84. Found C, 79.1; H, 9.45; N, 10.62.

**2,5-Dimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (41).** *N-iso*-propyl-α-*iso*-propylnitrone, **16** (1.00 g, 7.75 mmol), was dissolved under nitrogen in 20 mL of dry THF. A 3.0 M solution of phenylmagnesium bromide (5.17 mL, 15.5 mmol) in diethyl ether was added dropwise by cannula at room temperature over 2 min. The reaction mixture was then stirred at room temperature for 12 h, excess Grignard reagent was decomposed by the addition of 20 mL of concentrated ammonium chloride solution, and 10 mL of water was added until all of the solids dissolved. The organic layer was separated, and the aqueous layer was extracted with 10 mL of diethyl ether. The combined organic layers were then dried over magnesium sulfate, filtered, and concentrated in vacuo to give 1.57 g of crude hydroxyamine, **18a**, as a pale yellow oil. This compound was immediately used for the coupling reaction without further purification. Formation of the alkoxyamine, **41**, was achieved using the PbO$_2$ procedure defined above except that the crude hydroxyamine derivative was employed in the place of the nitroxide. This gave the alkoxyamine, **41**, which was purified by flash chromatography, eluting with 33:1 hexane/ethyl acetate, and obtained as a colorless oil (333 mg, 28% yield); TLC: 33:1 hexane/ethyl acetate, molybdenum stain, $R_f$ = 0.39, $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.6−6.9 (m, 20H), 5.0−4.8 (m, 2H), 3.1−2.8 (m, 2H), 2.5−2.2 (m, 2H), 1.54 (d, 3H), 1.6−1.1 (m, 6H), 1.03 (d, 3H), 1.0−0.8 (m, 15H), 0.75 (d, 3H); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 145.8 (s), 144.6 (s), 141.3 (s), 143.2 (s), 130.2 (d), 128.9 (d), 128.8 (d), 128.5 (d), 128.3 (d), 128.3 (d), 128.1 (d), 127.8 (d), 127.6 (d), 127.6 (d), 127.4 (d), 127.3 (d), 127.2 (d), 127.2 (d), 127.0 (d), 126.7 (d), 81.5 (d), 74.6 (d), 47.3 (d), 46.5 (d), 29.3 (d), 22.7 (q), 22.5 (q), 21.4 (q), 18.0 (q). HRMS exact mass calcd for [M + 1]$^+$ C$_{21}$H$_{29}$NO 311.2249, found 311.2252.

**2,5,5-Trimethyl-3-(1-phenylethoxy)-4-phenyl-3-azahexane (42).** The crude hydroxylamine, **18b**, was prepared from *N-iso*-propyl-α-*tert*-butylnitrone, **17**, and phenylmagnesium bromide as described above. This compound was immediately used for the coupling reaction without further purification. Formation of the alkoxyamine, **42**, was

achieved using the PbO$_2$ procedure as defined for **41**. This gave the alkoxyamine, **42**, which was purified by flash chromatography, eluting with 33:1 hexane/ethyl acetate and obtained as a colorless oil (515 mg, 55% yield); the coupling product was determined to be a 1:1.13 mixture of the diastereomeres as indicated by integration of the methyl hydrogens at δ 1.01 and 0.95 ppm; TLC: 50:1 hexane/ethyl acetate, molybdenum stain, $R_f$ = 0.39, $^1$H NMR (250 MHz, CDCl$_3$, both diastereomers) δ 7.7−7.1 (m, 20H), 5.1−4.9 (m, 2H, both diastereomers), 3.55 (s, 1H, major diastereomer), 3.40 (s, 1H, minor diastereomer), 1.54−1.49 (d + d, 6H, both diastereomers), 1.01 (s, 9H, minor diastereomer), 0.95 (s, 9H, major diastereomer), 0.9−0.6 (m, 6H, both diastereomers), 0.59 (d, 3H, $J$ = 6.5 Hz, minor diastereomer), 0.36 (d, 3H, $J$ = 6.5 Hz, major diastereomer); $^{13}$C NMR (APT) (63 MHz, CDCl$_3$, both diastereomers) δ 144.9 (s), 144.4 (s), 141.0 (s), 140.3 (s), 131.8 (d), 128.8 (d), 128.3 (d), 128.2 (d), 128.2 (d), 127.8 (d), 127.6 (d), 127.3 (d), 127.3 (d), 127.2 (d), 127.1 (d), 127.0 (d), 126.8 (d), 126.5 (d), 126.4 (d), 126.1 (d), 80.8 (d), 79.5 (d), 75.3 (d), 56.5 (d), 55.8 (d), 35.5 (s), 35.3 (s), 29.1 (q), 28.9 (q), 23.1 (q), 22.4 (q), 21.6 (q), 18.5 (q), 18.0 (q), 17.7 (q). HRMS exact mass calcd for [M + 1]$^+$ C$_{22}$H$_{31}$NO 325.2406, found 325.2409.

**General Procedure for Styrene Polymerization; Preparation of Polystyrene, 45, of DP = 250 from 29.** A mixture of the desired alkoxyamine, **29** (325 mg, 1.0 mmol), acetic anhydride (204 mg, 2.0 mmol), and styrene (26.0 g, 250 mmol) were degassed by three freeze/thaw cycles, sealed under argon, and heated at 125 °C under nitrogen for 8 h. The solidified reaction mixture was then dissolved in dichloromethane (50 mL) and precipitated (2×) into methanol (2 L). The precipitate was then collected by vacuum filtration and dried to give the desired polystyrene, **45**, as a white solid (23.1 g, 87.8% yield), $M_n$ = 23 000, PD = 1.08.

**General Procedure for Acrylate Polymerization; Preparation of Poly(*n*-butyl acrylate), 47, of DP = 250 from 29.** A mixture of the desired alkoxyamine, **29** (325 mg, 1.0 mmol), the corresponding nitroxide, **1** (11 mg, 0.05 mmol), and *n*-butyl acrylate (32.0 g, 250 mmol) were degassed by three freeze/thaw cycles, sealed under argon, and heated at 125 °C under nitrogen for 16 h. The viscous reaction mixture was then dissolved in dichloromethane (50 mL) and precipitated (2×) into methanol (2 L). The gummy precipitate was then collected

and dried to give the desired poly(*n*-butyl acrylate), **47**, as a colorless gum (26.9 g, 83.2% yield), $M_n$ = 24 000, PD = 1.09.

**General Procedure for Block Copolymer Formation; Preparation of Poly(*n*-butyl acrylate)-*b*-polystyrene, 48, from 29**. A mixture of the desired alkoxyamine, **29** (32.5 mg, 0.1 mmol), the corresponding nitroxide, **1** (1.1 mg, 0.005 mmol), and *n*-butyl acrylate (3.20 g, 25 mmol) were degassed by three freeze/thaw cycles, sealed under argon, and heated at 125 °C under nitrogen for 16 h. The viscous reaction mixture was then dissolved in dichloromethane (50 mL) and precipitated (2×) into methanol (2 L). The gummy precipitate was then collected and dried to give the desired poly(*n*-butyl acrylate), **47**, as a colorless gum (2.60 g, 80.4% yield), $M_n$ = 23 500, PD = 1.09. The poly(*n*-butyl acrylate), **47**, starting block (2.00 g, 0.085 mmol) was then redissolved in styrene (3.00 g, 28.8 mmol), acetic anhydride (17 mg, 0.17 mmol) was added, and the polymerization reaction mixture was heated at 125 °C for 8 h. The solidified reaction mixture was then dissolved in dichloromethane (10 mL) and precipitated (2×) into methanol (500 mL). The precipitate was then collected by vacuum filtration and dried to give the desired block copolymer, **48**, as a white solid (4.46 g, 89.2% yield), $M_n$ = 68 000, PD = 1.16.