JOC Article

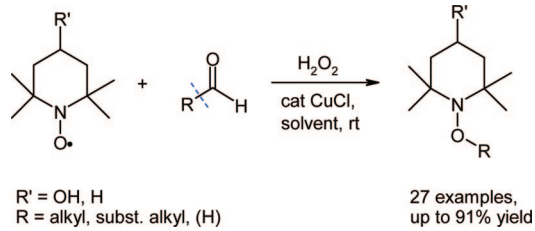
Synthetic Studies on *N*-Alkoxyamines: A Mild and Broadly Applicable Route Starting from Nitroxide Radicals and Aldehydes

Kai-Uwe Schoening,* Walter Fischer, Stefan Hauck, Alexander Dichtl, and Michael Kuepfert

Ciba Inc., WRO-1059, 4002 Basel, Switzerland

kai-uwe.schoening@ciba.com

Received October 28, 2008



A broad variety of 2,2,6,6-tetramethylpiperidine-based *N*-alkoxyamines were prepared in a newly found reaction. By means of a copper-catalyzed fragmentation reaction of aldehyde peroxides in the presence of TEMPO or TEMPO derivatives, *N*-alkoxyamines were obtained in moderate to good yields.

Introduction

N-Alkoxyamines (also termed alkoxyamines) derived from persistent sterically hindered aminoxyl radicals represent an important and rapidly developing class of organic compounds. They can be used not only as initiators for controlled radical polymerizations[1] but also as polymer light stabilizers, peroxide substitutes (rheology modifiers), or fireproofing agents.[2] There has been an ongoing interest in developing simple, selective, scalable, and cost-efficient methods for synthesizing diverse and functionalized analogues of this structural class starting from readily available precursors. However, most procedures conceived so far have not been able to fulfill these particular requirements for various reasons. The vast majority of syntheses known start from readily available nitroxide radicals, which are then reacted with carbon radicals, while only a few other approaches start from hydroxyl amines or oxoammonium salts. Quite naturally, the main focus of most investigations was to develop cheap and highly efficient methods for the generation of carbon radicals. These species can for instance be formed via treatment of alkanes with strong oxidizing agents[3] or iodides,[4] by reacting organo-peroxides with selected transition metal salts,[5] or via oxidation of organometallic compounds,[6] boronates,[7] or boranes.[8] Other well-known methods start from reactive esters such as malonates[9] or α-haloesters[10] or from haloalkanes,[11] hydrazides,[12] diazonium salts,[13] or haloalkyl-

(1) (a) Sciannamea, V.; Jerome, R.; Detrembleur, C. *Chem. Rev.* **2008**, *108*, 1104–1126. (b) Studer, A.; Schulte, T. *Chem. Rec.* **2005**, *5*, 27–35. (c) Hawker, C. J. In *Handbook of Radical Polymerization*; Matyjazewski, K., Davis, T. P.; Ed.; Wiley Interscience: Hoboken, 2002; pp 463−522. (d) Korolev, G. V.; Marchenko, A. P. *Russ. Chem. Rev.* **2000**, *69*, 409–434.

(2) (a) Pfaendner, R. *C. R. Chim.* **2006**, *9*, 1338–1344. (b) Robert, L. E.; Sanders, B. M.; Neri, C. *Annu. Tech. Conf.-Soc. Plast. Eng.* **1998**, *56*, 2880–2884.

(3) (a) Galbo, J. P.; Detlefsen, R. E. Hydrogen peroxide catalyzed alkoxylation of nitroxyl compounds to sterically hindered N-hydrocarbyloxyamines, especially N-hydrocarbyloxy-2,2,6,6-piperidines. PCT Patent Appl. WO 2005005388, 2005; CAN 142:155822. (b) Kirner, H.-J.; Schwarzenbach, F.; Van Der Schaaf, P. A.; Hafner, A.; Rast, V.; Frey, M.; Nesvadba, P.; Rist, G. *Adv. Synth. Catal.* **2004**, *346*, 554–560. (c) Winter, R. A. E.; Galbo, J. P.; Seltzer, R.; Behrens, R. A.; Mar, A.; Schirmann,P. J.; Malherbe, R. F. N-Substituted hindered amine stabilizers for coatings. Eur. Patent Appl. EP 309402,1998; CAN 112:79514.

(4) Frey, M.; Rast, V.; Martinez, F.; Alvisi, D. Process for the synthesis of sterically hindered *N*-alkoxyamines. PCT Patent Appl. WO 2006048389, 2006; CAN 144:468916.

(5) Sugimoto, N.; Narumi, A.; Satoh, T.; Kaga, H.; Kakuchi, T. *Polym. Bull.* **2003**, *49*, 337–340.

(6) (a) Shaver, M. P.; Allan, L. E. N.; Gibson, V. C. *Organometallics* **2007**, *26*, 4725–4730. (b) Thiessen, W.; Wolff, T. *Des. Monomers Polym.* **2005**, *8*, 397–407. (c) Stipa, P.; Greci, L.; Carloni, P.; Damiani, E. *Polym. Degrad. Stab.* **1997**, *55*, 323–327. (d) Braslau, R.; Burrill, L. C.; Siano, M.; Naik, N.; Howden, R. K.; Mahal, L. K. *Macromolecules* **1997**, *30*, 6445–6450.

(7) Cadot, C.; Dalko, P. I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. *J. Org. Chem.* **2002**, *67*, 7193–7202.

(8) Ollivier, C.; Chuard, R.; Renaud, P. *Synlett* **1999**, *6*, 807–809.

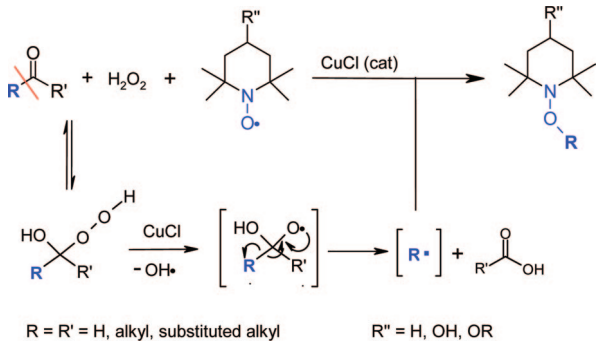
(9) Wetter, C.; Jantos, K.; Woithe, K.; Studer, A. *Org. Lett.* **2003**, *5*, 2899–2902.

(10) Matyjaszewski, K.; Spanswick, J. Process for preparation of alkoxyamines via a coupling reaction using a transition metal catalyst, an atom transfer radical polymerization (ATRP) initiator and a nitroxide or nitroxide precursor. PCT Patent Appl. WO 2007059350, 2007; CAN 147:9806.

(11) (a) Braslau, R.; Tsimelzon, A.; Gewandter, J. *Org. Lett.* **2004**, *6*, 2233–2235. (b) Couturier, J.-L.; Guerret, O. Method for preparing alkoxyamines from nitroxides. PCT Patent Appl. WO 2002012149, 2002; CAN 136:169419. (c) Couturier, J.-L.; Guerret, O. Method for preparing alkoxyamines from nitroxides. PCT Patent Appl. WO 2000061544, 2000; CAN 133:309685.

10.1021/jo802403j CCC: $40.75
Published on Web 01/12/2009

SCHEME 1. Plausible Reaction Mechanism for the Alkoxyamine Formation



benzenes.[14] Further methods involve ene-like additions of oxoammonium cations[15] or nitroxide radicals[16] to alkenes, the use of dithianes,[17] photolysis reactions,[18] S_N2-type reactions of alkoxides,[19] the reaction of nitrosoarenes with nitrogen oxides,[20] and even Meisenheimer-type rearrangements.[21] A comprehensive overview on state-of-the-art methods is given in a number of excellent reviews and monographs.[22]

Recently, we reported on the use of ketones and hydrogen peroxide to efficiently create alkyl radical precursors.[23] The copper(I) chloride-catalyzed decomposition of these peroxide intermediates in the presence of tetramethylpiperidine *N*-oxyl radicals represents a straightforward way to obtaining the desired alkoxyamines (Scheme 1).

Notwithstanding the fact that this reaction was successfully applied to synthesize a broad range of alkoxyamines, an element of limitation was the moderate selectivity in the radical transfer process (R vs R′). The problem was exacerbated by the fact that byproducts were formed in the reaction of α-oxo radicals with nitroxide radicals, which impaired the overall yield. We reasoned that these problems might be overcome by employing aliphatic aldehydes under the same reaction conditions (Scheme 1, R′ = H).

The known fact that aldehydes are less prone to oxidation in the presence of stable nitroxide radicals[24] was one important factor for this reaction to occur in a reliable fashion. Also, the reaction rate of the radical scavenging process by nitroxide radicals was so favorable that no homocoupling products were obtained in significant amounts. Thus, we were able to demonstrate that aldehydes are a superb source for the generation of intermediate alkyl radical species and eventually alkoxyamines.

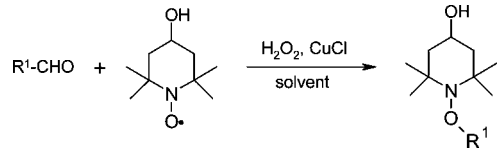
Results and Discussion

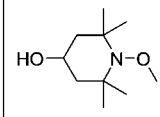
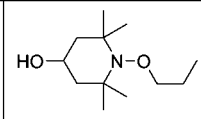
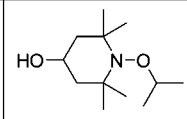
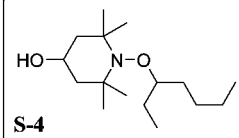
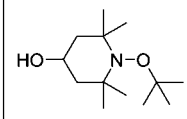
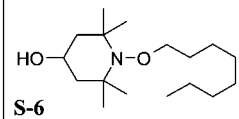
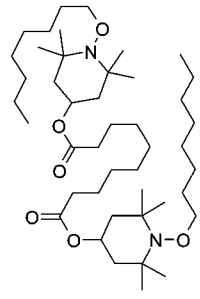
During our investigation into the formation of alkoxyamines we used 4-hydroxy-TEMPO (Prostab 5198)[25] as nitroxide radical, since this building block provided auspicious opportunities for subsequent chemical modifications.[26] When reacting mixtures of 4-hydroxy-TEMPO, catalytic amounts of copper(I) chloride, and various aldehydes with 30−50% aqueous hydrogen peroxide solution, we observed smooth conversions into the respective *N*-alkoxyamines. As depicted in Table 1, primary, secondary, and even tertiary aldehydes resulted in the anticipated products, whereby secondary and tertiary aldehydes seemed to give marginally smoother reactions. In most cases only small excesses (∼1.3 equiv) of aldehyde in relation to the nitroxyl radical were required to achieve satisfactory yields. However, in the case of acetaldehyde and longer chain aldehydes (>6 carbon atoms), higher amounts were necessary to obtain adequate yields. We attribute this behavior to the slightly higher sensitivity of these aldehydes toward oxidation. Also, the heat of formation in the case of **S-1** was significantly higher than with most other aldehydes. A larger aldehyde quantity was also required for the dimeric compound **S-7** in order to obtain a homogeneous product in a high yield.

The transformations presented were mostly executed between room temperature and 35 °C but may also be conducted at temperatures up to 45 °C (or even higher) to speed up the progress of the reactions. At higher temperatures the decomposition of hydrogen peroxide became rampant and necessitated higher dosages of the oxidant. In general, the reactions can be conducted with or without solvents. We learned that basically any solvent may be employed as long as it tolerates the presence of the oxidant. Among the solvents effectively tested were hexane, toluene, methyl *tert*-butyl ether, methylene chloride, alcohols, and water. Biphasic mixtures showed reaction rates comparable to those of homogeneous ones, though the use of phase-transfer catalysts proved to be advantageous in some cases. We also approached the question as to how much copper catalyst is required and which is the best one. Evidently, all copper sources catalyze the formation of alkoxyamines in this setup. In addition to the mentioned copper(I) chloride, other copper(I) salts promote the reaction equally well, independent of the solvent system used. By contrast, when the activity of copper(II) salts was evaluated, a clear solvent dependence was

(12) Braslau, R.; Anderson, M. O.; Rivera, F.; Jimenez, A.; Haddad, T.; Axon, J. R. *Tetrahedron* **2002**, *58*, 5513–5523.
(13) (a) Judd, D.; Shum, S. P.; Pastor, S. D. Polyoxometalate catalysts for the preparation of sterically hindered N-substituted aryloxyamines. US Patent 2003208071, 2003; CAN 139:350640. (b) Pastor, S. D.; Shum, S. P. Transition-metal-catalyzed preparation of sterically hindered N-substituted alkoxyamines and compositions. PCT Patent Appl. WO 2002079182, 2002; CAN 137:295596.
(14) Grubbs, R. B.; Wegrzyn, J. K.; Xia, Q. *Chem. Commun.* **2005**, *1*, 80–82.
(15) (a) Pradhan, P. P.; Bobbitt, J. M.; Bailey, W. F. *Org. Lett.* **2006**, *8*, 5485–5487. (b) Schaemann, M.; Chaefer, H. J. *Synlett* **2004**, *9*, 1601–1603.
(16) (a) Dufils, P.-E.; Chagneux, N.; Gigmes, D.; Trimaille, T.; Marque, S. R. A.; Bertin, D.; Tordo, P. *Polymer* **2007**, *48*, 5219–5225. (b) Schulte, B.; Studer, A. *Synthesis* **2006**, *13*, 2129–2138. (c) Wetter, C.; Studer, A. *Chem. Commun.* **2004**, *2*, 174–175.
(17) Herrera, A. J.; Studer, A. *Synthesis* **2005**, *9*, 1389–1396.
(18) Bertin, D.; Couturier, J. L.; Gigmes, D.; Guerret, O.; Guillaneuf, Y. Process for preparation of alkoxyamines by photolysis of dithiocarbamates. Fr. Patent FR 2884517, 2006; CAN 145:421104.
(19) Moon, B.; Kang, M. *Macromol. Res.* **2005**, *13*, 229–235.
(20) Astolfi, P.; Carloni, P.; Damiani, E.; Greci, L.; Marini, M.; Rizzoli, C.; Stipa, P. *Eur. J. Org. Chem.* **2008**, *19*, 3279–3285.
(21) (a) Zedda, A.; Ferri, G.; Sala, M. Production of steric hindered cyclic amine ethers for stabilizers for polymers. Ger. Patent DE 19907945, 1999; CAN 131:185784. (b) Bergbreiter, D. E.; Walchuk, B. *Macromolecules* **1998**, *31*, 6380–6382. (c) Tabushi, I.; Hamuro, J.; Oda, R. *Tetrahedron Lett.* **1968**, *53*, 5581–5584.
(22) (a) Sciannamea, V.; Jerome, R.; Detrembleur, C. *Chem. Rev.* **2008**, *108*, 1104–1126. (b) Nesvadba, P. *Chimia* **2006**, *12*, 832–840. (c) Bertin, D.; Gigmes, D.; Marque, S. R. A. *Recent Res. Dev. Org. Chem.* **2006**, *10*, 63–121. (d) Studer, A.; Schulte, T. *Chem. Rec.* **2005**, *5*, 27–35. (e) Studer, A. *Chem. Soc. Rev.* **2004**, *33*, 267–273. (f) Togo, H. *Advanced Free Radical Reactions for Organic Synthesis*, 1st ed.; Elsevier: Amsterdam, 2004. (g) Tirrell, D. A. *J. Polym. Sci., Part A: Polym. Chem.* **1998**, *36*, 2667–2668. (h) Volodarsky, L. B.; Reznikov, V. A.; Ovcharenko, V. I. *Synthetic Chemistry of Stable Nitroxides*; CRC Press: Boca Raton, 1994.
(23) (a) Dichtl, A.; Seyfried, M.; Schoening, K.-U. *Synlett* **2008**, *12*, 1877. (b) Schoening, K.-U.; Fischer, W.; Basbas, A.-I.; Dichtl, A. Process for the preparation of sterically hindered nitroxyl ethers. PCT Patent Appl. WO 2008003602, 2008; CAN 148:144654.
(24) Minisci, F.; Recupero, F.; Cecchetto, A.; Gambarotti, C.; Punta, C.; Faletti, R.; Paganelli, R.; Pedulli, G. F. *Eur. J. Org. Chem.* **2004**, *1*, 109–119.
(25) Commercial Product of Ciba Inc.
(26) The same reactions were also conducted with TEMPO, but because of limited options for further chemical transformations this nitroxide radical is of little use in industrial applications.

TABLE 1. Reaction of Aliphatic Aldehydes with 4-Hydroxy TEMPO



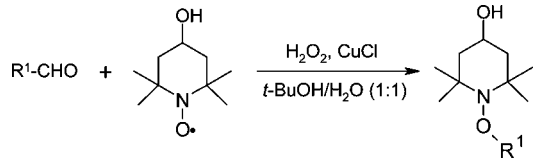
entry	R^1	aldehyde (equiv)	H_2O_2 (equiv)	CuCl (mol%)	product	time (h)	T (°C)	yield (%)[a]
1	Methyl	4	3	2	 **S-1**	5	70	72[b]
2	1-Propyl	1.5	1.35	1	 **S-2**	15	35	84[c]
3	2-Propyl	1.5	1.5	2	 **S-3**	12	20	91[d]
4	3-Heptyl	solvent	1.5	2.5	 **S-4**	16	30	75
5	*t*-Butyl	1.25	1.5	2	 **S-5**	17	20	85[e]
6	1-Octyl	3.5	2.6	2.5	 **S-6**	17	40	71[f]
7	1-Octyl	5	5	1.25	 **S-7**	15	40	75[g]

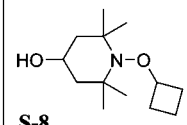
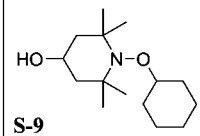
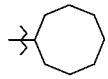
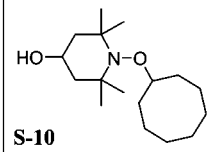
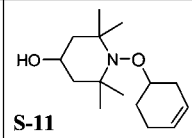
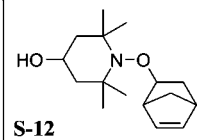
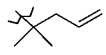
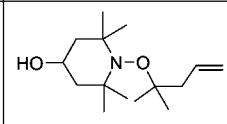
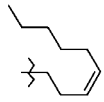
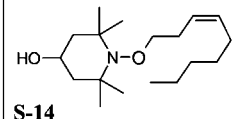
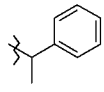
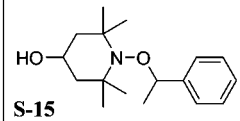
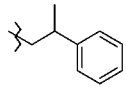
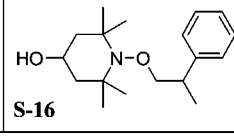
[a] Isolated yield. [b] Reaction performed in H_2O. [c] Reaction performed in 1-BuOH/H_2O (4:1). [d] Reaction performed in 2-PrOH/H_2O (1:5). [e] Reaction performed in EtOH/H_2O (1:1). [f] Reaction performed in *t*-BuOH/H_2O (2:1). [g] Reaction performed in heptane/*t*-BuOH (4:1).

found: in polar systems the counterion had essentially no effect on the conversion rate, but in apolar systems most copper(II) catalysts showed an inferior performance. The same held true for elementary copper, which was successfully used in systems where it was allowed to gradually dissolve. Optimal catalyst amounts were determined to be between 1 and 3 mol % in relation to the amount of nitroxide radical employed.

Next, we investigated the transformation of cycloaliphatic aldehydes (entries 8−10, Table 2), and apparently these substrates were less reactive than their acyclic counterparts. From C-4 toward C-8 carbaldehydes we observed increasing yields, and the optimum seemed to be at C-6. The below average yield of **S-8** may be explained by increased concomitant carboxylic acid formation or decomposition of the aldehyde. The reaction of cyclopropyl carbaldehyde and related aldehydes was also investigated, but we were unable to isolate the corresponding products; traces of the compounds were detectable by mass spectrometry only. During the investigation of the ring

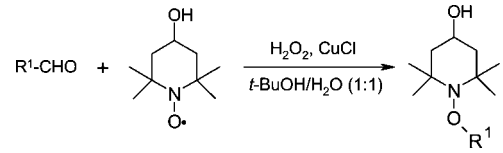
TABLE 2. Reaction of Cycloaliphatic and Unsaturated Aldehydes with 4-Hydroxy TEMPO

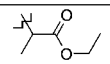
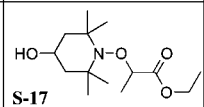
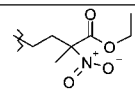
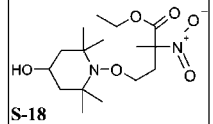
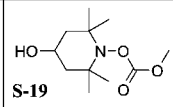
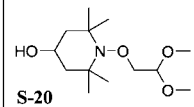
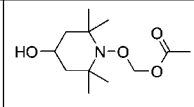
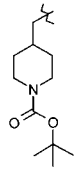
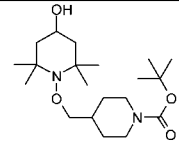
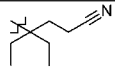
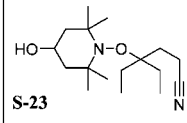
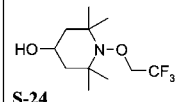
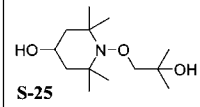
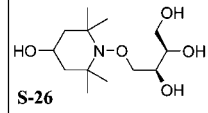
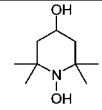


entry	R^1	aldehyde (equiv)	H_2O_2 (equiv)	CuCl (mol%)	product	time (h)	T (°C)	yield (%)[a]
8		1.3	1.9	3.5	 **S-8**	22	40	24
9		1	2	1[f]	 **S-9**	23	30	62
10		1.3	1.5	3.5	 **S-10**	42	20	45
11		1.5	1.6	1	 **S-11**	13	30	72[b]
12		1.5	1.5	2.5	 **S-12**	48	20	74[c]
13		1.3	1.5	3.5	 **S-13**	28	20	84
14		3.9	1.5	3.5	 **S-14**	29	20-40	61
15		2	2	3.5	 **S-15**	13	20	68[d]
16		1.3	1.5	3.5	 **S-16**	12	20	68[e]

[a] Isolated yield. [b] Reaction performed in *t*-BuOH/H_2O (2:1). [c] Reaction performed in EtOH. [d] Reaction performed in *t*-BuOH. [e] Reaction performed in H_2O. [f] $CuCl_2$ used as catalyst.

TABLE 3. Synthesis of Functionalized Alkoxyamines



entry	R^1	aldehyde (equiv)	H_2O_2 (equiv)	CuCl (mol%)	product	time (h)	T (°C)	yield (%)[a]
17		1.3	1.5	3.5	 **S-17**	26	30	63
18		1.5	1.5	5	 **S-18**	22	20	64
19		solvent	1.35	2	 **S-19**	13	20	76
20		solvent	1.35	2	 **S-20**	10	20	66
21		2	2	2	 **S-21**	14	20	68[b]
22		1.3	2.7	5	 **S-22**	21	20	40
23		1.3	1.5	3.5	 **S-23**	43	20-40	61
24		1.3	1.5	3.5	 **S-24**	72	20	74
25		1.3	1.25	3.5	 **S-25**	13	20	69
26		0.85	1.2	2.7	 **S-26**	16	30	38[c]
27	H	solvent	1.5	0.85	 **S-27**	16	30	87

[a] Isolated yield. [b] Reaction performed in toluene. [c] Reaction performed in HOAc/H_2O (3:1).

systems, we also employed 3-cyclohexene-1-carboxaldehyde, which was found to react without accompanying side reactions at the olefinic position (**S-11**). A deeper evaluation of the scope and limitation of olefins revealed that many unsaturated aldehydes may be used in this coupling reaction. Except for α, β and α, β, γ, δ unsaturated aldehydes, most aldehydes tested yielded the envisioned products irrespective of the position or the substitution pattern of the double bonds (entries 11−14).

Alkoxyamines bearing benzylic substituents are of particular interest as polymerization initiators. The relevant phenethyl-substituted product (entry 15) was accordingly prepared,[27] as well as the CH_2-elongated homo product (entry 16), both without formation of noteworthy byproduct. However, the presumption that benzaldehyde(s) would react likewise proved to be wrong, as we were not able to prepare the corresponding phenoxy tetramethylpiperidines. We ascribe this result to the insufficient electrophilicity of many aromatic aldehydes so that the hydrogen peroxide does not readily add to the carbonyl group. Nevertheless, it may be possible, by choosing appropriate aryl substitutents, to form benzyl hydroperoxides[28] and, ultimately, phenyl radicals.

As discussed earlier, this coupling protocol appears quite mild compared to other alkoxyamine-forming reactions, and so far we have gathered mounting evidence that a much broader range of aldehydes (and in particular functionalized ones) ought to be applicable in this reaction. First, we investigated the use of ester-substituted aldehydes (Table 3, entries 17 and 18). Again, neither the presence of a substituent in α-position nor the presence of a nitro group interfered with the reaction,[29] and even carbonates were formed quite smoothly (entry 19). The next challenge was to form acetal-containing alkoxyamines (entries 20 and 21), because the required precursors as well as the products are more labile than esters and prone to peroxide attack.[30] We were pleased to find that the conjectured products formed equally well. Furthermore, carbamate protecting groups (entry 22) were tolerated as well as nitriles (entry 23). The latter one was particularly surprising since nitriles are known to readily interact with hydrogen peroxide to form transient peroxyimidates or peroxycarboximidic acids. The fact that β-fluoro aldehydes (entry 24) were decent substrates (in contrast to α-substituted ones, cf. ref 23) did not take us by surprise. Finally, we investigated the behavior of hydroxy-substituted aldehydes. We envisioned that sterically hindered alcohols would work best (entry 25) because the possibility of concomitant side reactions would be limited, and we were surprised to discover that even hydroxy aldehydes that prevail as hemiacetals (entry 26) formed the anticipated products in modest yields. However, more complex sugars such as glucose did not give any conversion, presumably due to copper complexation.

A particularly interesting product was **S-27**, which was formed in a formal reduction reaction under oxidative conditions. Evidently, formaldehyde was capable of following the same reaction pathway as most other aldehydes and correspondingly provided the free hydroxylamine in a straightforward fashion. To the best of our knowledge, this is the first time that a radical-induced reduction using formaldehyde is reported.

Conclusions

We have presented a broadly applicable and extraordinary mild reaction for the formation of *N*-alkoxyamines. It stands out from the mass of methods available because cheap or readily available nontoxic precursors are used and particularly, a broad range of functional groups is tolerated. Also, the method allows all reactions to be performed in wet solvents and under an aerobic atmosphere, thus offering a high operational simplicity. Although reactive carbon radicals are evidently generated in this process, the number and amount of isolatable byproduct is almost negligible.[31] This is particularly important if an industrial large-scale application is considered. It appears that the radicals are somewhat tamed so as to not display their full reaction potential, e.g., in terms of H-radical abstraction or homocoupling. The relatively small excesses of aldehyde and H_2O_2 necessary to achieve a full nitroxide radical conversion point into the same direction. We speculate that this reduced reactivity might be the result of intermediary Cu-complexes of the type $[Cu^{I}\text{-}OOC(OH)R]$[32] or connatural intermediates that do not decompose until coming into contact with the nitroxide radical.

As the successful usage of more complex aldehydes pointed out, this method may also be adoptable in natural product synthesis and redundantize or allow the use of particular protecting groups, or may be applicable to the preparation of new spin-label precursors. In addition, this method could open up new opportunities in the field of living radical polymerization, as entirely new initiators may be accessible by the use of accordingly substituted aldehydes. In particular in combination with the complementary ketone option this reaction has an enormous potential.

The method presented is not fully optimized yet, and we are convinced that by carefully choosing the parameters temperature, amounts of aldehyde and hydrogen peroxide, and solvent higher yields and/or conversion rates can be achieved. Moreover, the full potential in terms of synthetic applications has not been discovered yet. So it may well be possible to synthesize alkoxyamines with a predictable temperature stability by an accurate choice of the type of nitroxyl radical and the aldehyde.

A final comment should be made with regard to the *safety* of this process: as the combination of hydrogen peroxide and organic matter always poses the risk of uncontrollable decomposition reactions, adequate safety measures should be applied when conducting this reaction. In particular, a peroxide test should be carried out after the workup process (before solvent removal) and before conducting distillations.

Experimental Section

Representative Procedures for the Synthesis of Alkoxyamines. 1-Methoxy-2,2,6,6-tetramethylpiperidin-4-ol (S-1). To a solution of 5.0 g (29.0 mmol) of 4-hydroxy-TEMPO in 20 mL of water was added CuCl (57 mg, 2 mol %) and acetaldehyde (6.6 mL, 116 mmol). Next, 8.9 mL (87 mmol) of 30% H_2O_2 was added

(27) Alkoxyamines based on the 2,6-diethyl-4-hydroxy-2,3,6-trimethylpiperidine-1-*N*-oxyl core were also prepared. As a result of the higher sterical hindrance, prolonged reaction times were observed.

(28) (a) Rakhimov, A. I.; Chapurkin, V. V. *Zh. Org. Khim.* **1981**, *17*, 1546–7. (b) Rakhimov, A. I.; Chapurkin, V. V. *Zh. Org. Khim.* **1978**, *14*, 204.

(29) Zelentsov, S. V.; Simdyanov, I. V. *Russ. Chem. Bull.* **2006**, *55*, 207–211.

(30) Rieche, A. *Chem. Ber.* **1961**, *94*, 2457–61.

(31) Typical byproducts of this process were 4-oxo-alkoxyamines and C-1-shortened carbon chain homologues of the respective products in small amounts. The former ones can be transformed into the desired product by means of a sodium borohydride treatment during the workup process; the latter ones usually do not have a negative impact on subsequent chemistry. In addition, 1-hydroxy-2,2,6,6-tetramethyl-4-piperidinol and 2-methyl-2-penten-4-one were formed and were removed during the workup process. Among the gaseous byproducts carbon dioxide and, in some cases, olefins (generated via β-H radical elimination of the respective alkyl radicals) were identified by GC−MS.

(32) Hong, S.; Huber, S. M.; Gagliardi, L.; Cramer, C. C.; Tolman, W. B. *J. Am. Chem. Soc.* **2007**, *129*, 14190–14192.

over a period of 30 min while keeping the temperature at 65−70 °C. After 4 h of stirring at this temperature, the mixture was slowly cooled to room temperature while the product started to precipitate. The pH of the reaction mixture was adjusted to ∼8 using 10% K_2CO_3 solution, and the mixture was cooled to 5 °C. The product was collected by filtration. The filter cake was washed successively with cold 10% ascorbic acid solution and water. The filtrate was extracted with toluene, and the organic phase was washed with brine. Upon drying over Na_2SO_4, the organic phase was removed in vacuo to yield a tan residue. The combined crude product fractions were purified by distillation (0.04 mbar, 120 °C oil bath temp, bp ∼90 °C) to give **S-1** as a white solid (3.9 g, 20.8 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.94 (m, 1H), 3.61 (s, 3H), 1.79 (dd, J = 12.0, 4.0 Hz, 2H), 1.64 (br s, 1H), 1.46 (ps t, J = 12.0 Hz, 2H), 1.21 (2s, 6H), 1.26 (2s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 65.4 (t), 63.2 (2q), 60.0 (p), 48.2 (2s), 33.1 (2p), 20.9 (2p). IR (neat): ν_{max} 3265, 2960, 1450, 1358, 1173, 1026 cm^{-1}. MS: m/z = 188 [M + H]$^+$. Anal. Calcd for $C_{10}H_{21}NO_2$: C, 64.13; H, 11.30; N, 7.48. Found: C, 63.94; H, 11.22; N, 7.45.

1-Propoxy-2,2,6,6-tetramethylpiperidin-4-ol (S-2). To a mixture of 150.0 g (870.8 mmol) of 4-hydroxy-TEMPO in 620 mL of 1-butanol/water (1:4) were added CuCl (861 mg, 1 mol%) and butanal (94.2 g, 1.31 mol). Next, 120 mL (1.18 mol) of 30% H_2O_2 was added over a period of 30 min while keeping the temperature between 30 and 35 °C. Stirring was continued at 35 °C for 8 h, whereupon another 12 mL (118.0 mmol) of H_2O_2 was added. After 6 h the reaction mixture was extracted with MTBE. The combined organic phases were washed with 2 N NaOH, water, 5% Na_2EDTA, 10% ascorbic acid solution, and brine. After drying over Na_2SO_4, the organic phase was concentrated in vacuo to provide an off-white solid. Pure **S-2** was obtained after column chromatography (silica gel, hexane/acetone 9:1) (157.5 g, 731.5 mmol, 84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.95 (m, 1H), 3.70 (q, J = 9.2 Hz, 2H), 1.80 (dd, J = 14.4, 3.2 Hz, 2H), 1.70 (br s, 1H, OH), 1.50 (m, 4H), 1.24 (2s, 6H), 1.15 (2s, 6H), 0.95 (t, J = 10.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 78.4 (s), 63.3 (t), 60.0 (2q), 48.3 (2s), 33.2 (2p), 21.9 (s), 21.0 (2p), 10.9 (p). IR (neat): ν_{max} 3264, 2965, 1451, 1363, 1173, 1040 cm^{-1}. MS: m/z = 216 [M + H]$^+$. Anal. Calcd for $C_{12}H_{25}NO_2$: C, 66.93; H, 11.70; N, 6.50. Found: C, 66.73; H, 11.59; N, 6.38.

4-Hydroxy-2,2,6,6-tetramethylpiperidin-1-yl Carbonic Acid Methyl Ester (S-19). To a solution of 2.5 g (14.5 mmol) of 4-hydroxy-TEMPO in 8 g (90.8 mmol) of methyl glyoxylate was added CuCl (28.7 mg, 2 mol%). Next, 2.0 g (19.6 mmol) of 30% H_2O_2 was added over a period of 60 min. After 12 h of stirring at room temperature, the mixture was diluted with MTBE. The organic phase was washed with 10% ascorbic acid solution, 1 N NaOH, water, and brine. After drying over $MgSO_4$, the organic phase was concentrated under vaccum to leave a white solid. The crude product was filtered over silica gel using hexane/acetone (2:1) as the eluent to yield **S-19** as a white solid (2.55 g, 11.0 mmol, 76%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.01 (m, 1H), 3.82 (s, 3H), 1.89 (dd, J = 11.2, 4.2 Hz, 2H), 1.82 (br s, 1H), 1.67 (ps t, J = 11.2 Hz, 2H), 1.21 (2s, 6H), 1.15 (2s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (q), 63.1 (t), 61.1 (2q), 55.5 (p), 48.1 (2s), 32.0 (2p), 21.6 (2p). IR (neat): ν_{max} 3234, 2966, 1773, 1440, 1365, 1225, 1183, 1047 cm^{-1}. MS: m/z = 232 [M + H]$^+$. Anal. Calcd for $C_{11}H_{21}NO_4$: C, 57.12; H, 9.15; N, 6.06. Found: C, 57.34; H, 8.97; N, 5.83.

Acknowledgment. The authors thank the Ciba Research Analytics group (Coating Effects Segment) and the Ciba Expert Services Group, Switzerland for their support.

Supporting Information Available: Experimental procedures and ^{1}H, ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO802403J