Factors Influencing the C−O Bond Homolysis of Alkoxyamines: Effects of H−Bonding and Polar Substituents

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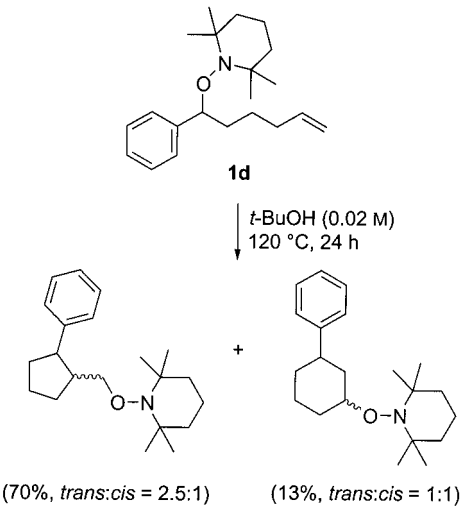
The synthesis of various new trialkylhydroxylamines is described. The rate constant of the C−O bond cleavage of these new alkoxyamines has been measured. For example, C−O bond homolysis rates in a series of para-substituted TEMPO-styryl compounds TEMPO-CH(CH_3)C_6H_5X **1a** (*p*-MeO), **1b** (*p*-Me), **1d** (*p*-H), **1e** (*p*-Br), and **1f** (*p*-MeO_2C) are presented. Furthermore, rate constants for the C−O bond cleavage of α-heteroaryl-substituted secondary alkoxyamines are discussed. A correlation by which the rate constant for the C−O bond cleavage of TEMPO-derived alkoxyamines can be predicted from the C−H BDEs of the corresponding alkanes is presented. Solvent effects as well as the effect of camphorsulfonic acid on the rate of the C−O bond homolysis are discussed. Finally, EPR and kinetic evidence show that alkoxyamines derived from nitroxides which are capable of intramolecular H-bonding undergo C−O bond cleavage faster than the corresponding non-H-bond-forming analogues.

Introduction

In seminal work, Rizzardo et al. and later Georges et al. have demonstrated that polymers with polydispersities well below the theoretical limit of 1.5 can be prepared by nitroxide-mediated living radical polymerization.[1] Since then, many groups have further extended this concept for the preparation of well-defined polymers.[2] These processes are controlled by the so-called persistent radical effect (PRE).[3,4] The PRE is a general principle that explains the specific coupling of a persistent and a transient radical when they are formed with equal rates. There is a buildup of the persistent radical with respect to the transient counterpart which is due to self-termination of the latter and leads to a highly selective reaction of the transient with the persistent radical.

Scheme 1. Radical Cyclization Reaction Using the PRE



Very recently, we presented first results on radical cyclization reactions using the PRE.[5] Nitroxides have been used as persistent radicals in these processes. For example, the 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO)-derived alkoxyamine **1d** was readily isomerized to the corresponding 5-exo (70%) and 6-endo (13%) cyclization products (Scheme 1). Furthermore, we introduced new nitroxides, capable of intramolecular hydrogen bonding. Careful kinetic analysis[4] showed that the rate constant of the C−O bond homolysis of the alkoxyamine is a very

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important parameter in reactions of this type.[6] In this work, we present the preparation of various new alkoxyamines in full details. Moreover, we report rate constants for the C−O bond homolysis of these alkoxyamines under different conditions. The effect of the para substituent in various TEMPO-styryl derivatives will be discussed. Furthermore, we provide evidence that alkoxyamines derived from nitroxides which are capable of intramolecular hydrogen bonding homolyze faster to the corresponding radicals than their non-H-bond-forming analogues. In addition, EPR data of new nitroxides will be reported. The knowledge of the rate constants of the C−O bond homolysis is essential for synthetic planning of nitroxide-mediated tin-free radical chemistry and living free radical polymerizations.

Results and Discussion

Preparation of the Alkoxyamines. In Figure 1, all the alkoxyamines studied in this work are presented. The alkoxyamines **1a**,**d**,**e** were prepared by reacting the sodium salt of 1-hydroxy-2,2,6,6-tetramethylpiperidine (TEMPO-Na) with the corresponding bromide in refluxing THF for 14−20 h (20−80%).[7] The phenylsulfanyl-substituted alkoxyamine **1j**, the pyridyl derivative **1g,** and the thienyl-substituted alkoxyamine **1h** were synthesized in analogy using (1-chlorohex-5-enylsulfanyl)-benzene,[8] 1-mesyloxy-1-(2-pyridyl)-5-hexene, and 1-bromo-1-(2-thienyl)-5-hexene, respectively. For alkoxyamine **1j**, 4-*tert*-butyldimethylsilyloxy-TEMPO was used instead of TEMPO. Desilylation was performed using HF·pyridine in CH_2Cl_2 to eventually afford the hydroxy-TEMPO derivative **1j**. Alkoxyamine **2c** was prepared from commercially available *N*,*N*-di-*tert*-butylnitroxide and 1-bromo-1-phenyl-5-hexene by the same method.

Deprotonation of 6-cyano-1-hexene by lithium diisopropylamide (LDA, −78 °C) and subsequent addition of a suspension of $CuCl_2$ and TEMPO in THF afforded after workup and purification nitrile **1l** in 61% yield.[9] The acylated TEMPO derivative **1i** was readily available by reaction of phenylacetic acid chloride with the sodium salt of TEMPOH in THF in the presence of a catalytic amount of dimethylaminopyridine (DMAP, 89%).

The alkoxyamines **1k**, **2a**, and **7b** were synthesized from 6-iodo-6-methyl-1-heptene according to Boger[10] by treatment of the iodide in refluxing benzene with the corresponding nitroxide and tributyltin hydride. The nitroxide used for the preparation of **7b** has previously been described.[11] Triol **8c** was obtained by ortho ester deprotection of **7b** using standard procedures (see the Experimental Section).

The alkoxyamines **1b**, **1f**, **3a**, **5**, and **7a** were prepared from the corresponding benzylic bromides using a procedure reported by Matyjaszewski.[12] Thus, a benzene suspension containing the bromide, the nitroxide, copper powder, and a catalytic amount of copper bistriflate and 4,4′-di-*tert*-butyl-2,2′-bipyridine was stirred for 5−10 h at 70 °C. Removal of the solids by filtration and subsequent purification by chromatography (SiO_2) afforded **3a**, **5**, and **7a** as a mixture of diastereoisomers (dr ≈ 1:1). Similar alkoxyamines have previously been applied as initiators in nitroxide-mediated polymerizations.[13] Triol **8a** was easily obtained from **7a** after ortho ester deprotection. Alkoxyamine **8b** was prepared in analogy. The Cu method was also applied for the synthesis of **4** and **6** as specified in the Experimental Section. The decay of the alkoxyamines **1c**, **2b**, and **3b** has previously been

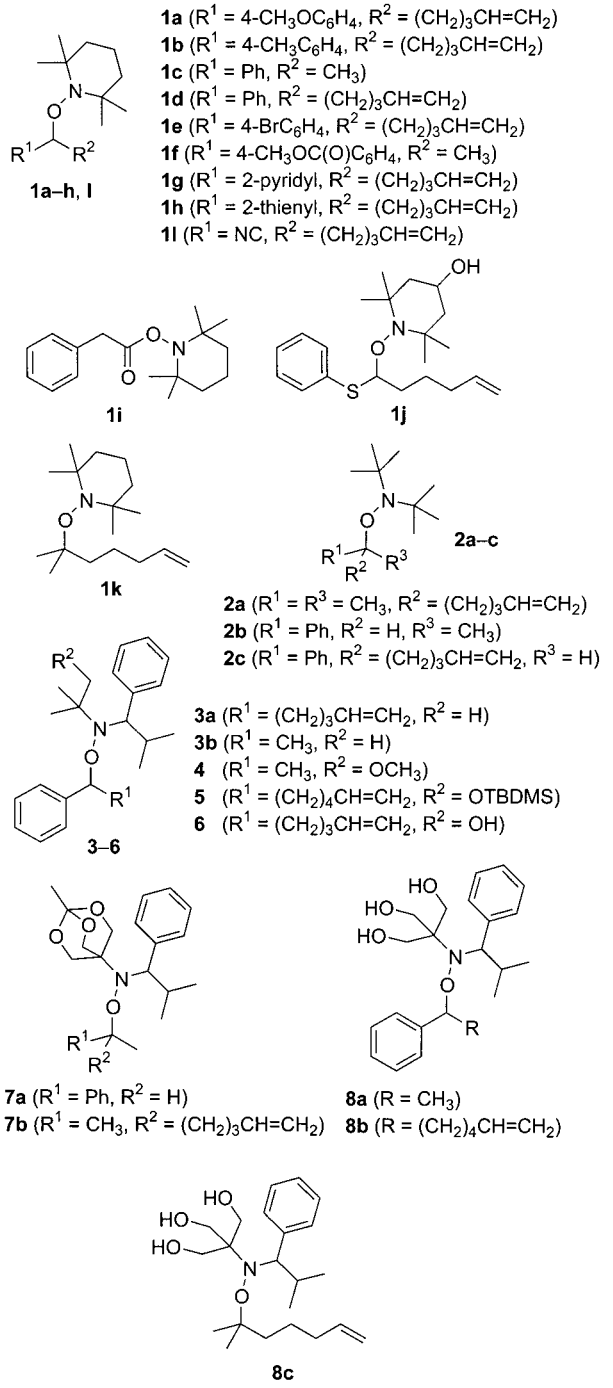

Figure 1. Various alkoxyamines studied.

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Table 1. Activation Parameters and Rate Constants at 120 °C for the Dissociation of the C−O Bond in Trialkylhydroxylamines (NO-R)

entry	NO-R	runs	T (°C)	A^a (10^{14} s^{-1})	E_a (kJ·mol^{-1})^b	k_d (s^{-1})	k_d^{Me} ^{c} (s^{-1})	ref
1	**1a**	3	119−140	-	132.8 (est)	5.3×10^{-4}	4.2×10^{-4}	
2	**1b**	7	105−135	1.2	129.7	6.9×10^{-4}	5.5×10^{-4}	
3	**1c**	17	90−150	2.5	133.0	5.2×10^{-4}	*d*	6
4	**1d**	3	130−151	-	131.9 (est)	7.0×10^{-4}	5.6×10^{-4}	
5	**1e**	5	110−150	0.9	127.2	1.1×10^{-3}	8.8×10^{-4}	
6	**1f**	7	95−130	1.1	126.6	1.6×10^{-3}	*d*	
7	**1g**	8	94−130	2.1	129.7	1.2×10^{-3}	9.6×10^{-4}	
8	**1h**	7	79−129	0.1	112.4	1.2×10^{-2}	9.6×10^{-3}	
9	**1i**	2	150.8	-	175.7 (est)	1.1×10^{-9}		
10	**1j**^{e}	3	150.5	-	162.7 (est)	5.1×10^{-8}	4.1×10^{-8}	
11	**1k**	3	130−151	-	144.0 (est)	1.3×10^{-5}	1.0×10^{-5}	
12	**1l**	7	100−152	8.9	137.9	4.3×10^{-4}	3.4×10^{-4}	
13	**2a**	2	99−120		134.6 (est)	3.1×10^{-4}	2.5×10^{-4}	
14	**2b**	13	60−129	2.2	121.8	1.4×10^{-2}	*d*	6
15^f	**2c**	1	100.0	-	119.1 (est)	3.5×10^{-2}	2.8×10^{-2}	
16	**3a**^{g}	3	110−130	-	127.1 (est)	3.0×10^{-3}	2.4×10^{-3}	
17	**3b**	10	60−131	5.6	129.6	3.3×10^{-3}	*d*	6
18	**4**^{h}	7	100−130	-	129.8 (est)	1.3×10^{-3}	*d*	
19	**5**^{h}	5	110−131	-	127.1 (est)	3.0×10^{-3}	2.4×10^{-3}	
20	**6**^{i}	3	110−131	-	126.5 (est)	3.6×10^{-3}	2.9×10^{-3}	
21	**7a**^{h}	6	120−131	-	136.9 (est)	1.5×10^{-4}	*d*	
22	**7b**	3	119−132	-	152.8 (est)	1.2×10^{-6}	9.6×10^{-7}	
23	**8a**^{h}	5	115−124	-	125.1 (est)	5.6×10^{-3}	*d*	
24	**8b**^{h}	3	120−126	-	124.1 (est)	7.6×10^{-3}	6.1×10^{-3}	
25	**8c**	5	110−130	-	139.1 (est)	7.9×10^{-5}	6.3×10^{-5}	

^{a} Statistical errors smaller than a factor of 2. ^{b} Statistical errors between 2 and 3 kJ·mol^{-1}. ^{c} Corrected rate constants (20% reduction) for alkoxyamines with longer alkyl chains; see text. ^{d} No correction necessary. ^{e} 4-Hydroxy-TEMPO was used instead of TEMPO. ^{f} In *t*-BuPh/*t*-BuOH (1:1). ^{g} Mixture of diastereoisomers (65:35). ^{h} Mixture of diastereoisomers (1:1). ^{i} Mixture of diastereoisomers (54:46).

analyzed[6] and is included in the present paper for comparison.

Determination of the Rate Constant of the C−O Bond Homolysis. The experimental cleavage rate constants k_d were measured using the plateau (eq 1) or the initial slope (eq 2) of the growing EPR nitroxide signal in the presence of alkyl radical scavengers such as dioxygen or 2,2,10,10-tetraperdeuteriomethylisoindolin-^{15}N-oxyl (TMIO-$^{15}ND_{12}$) as previously described.[6]

$$\ln\left(\frac{[\text{nitroxide}]_\infty - [\text{nitroxide}]_t}{[\text{nitroxide}]_\infty}\right) = -k_d t \qquad (1)$$

$$[\text{nitroxide}]_t/[\text{nitroxide}]_\infty = k_d t \qquad (2)$$

The kinetic experiments were carried out in *tert*-butylbenzene. We[6] and others[14] have already shown that O_2 is a reliable alkyl radical scavenger in alkoxyamine homolysis experiments.[15] In the present work, most of the kinetic experiments were performed with O_2 as the scavenger. Results are reproducible, and rate constants do not change upon varying the alkoxyamine concentration. For the phenylsulfanyl-substituted alkoxyamine **1j**, however, slightly different rate constants at different concentrations were obtained. Probably some side reactions due to the presence of the phenylsulfanyl group occurred.[16] For the nitroxides **5** and **6**, the rate constants k_d were also determined using TMIO-$^{15}ND_{12}$ as alkyl radical scavenger. The results of the TMIO-$^{15}ND_{12}$-experiments are in fair agreement with the results obtained by O_2-scavenging. In the homolysis experiments of the alkoxyamines **4**−**6**, **8a**, and **8b**, *N*-(2-methyl-1-phenylpropyl)-*N*-(1-methyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl)-*N*-oxyl (**7′**) and *N*-(*tert*-butyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl (**3′**) were used as a standard because the corresponding free nitroxides were not available (see Figure 5).

We have shown earlier, that the frequency factor A of the C−O-bond homolysis of various alkoxyamines (15 different compounds studied) does not vary much with alkoxyamine structure but lies between 10^{13} and 10^{15} s^{-1} with an average value of 2.6×10^{14} s^{-1}.[6] Here, we present Arrhenius parameters for six new alkoxyamines (Table 1; the Arrhenius parameters were determined from the k_d values at various temperatures using a nonlinear least-squares (NLLS) method). With the exception of **1h**, the frequency factors are in the above region.

Our activation energies and frequency factors are somewhat different from earlier data.[4c] This may be due to the well-known and unavoidable error compensation effect of the activation parameters as discussed in our previous paper.[6,17] To circumvent this problem, the discussions in the present paper are mainly based on differences of the homolysis rate constants for the various alkoxyamines. For those alkoxyamines, where the rate constant was determined only at a few temperatures, the activation energies E_a were estimated from the rate constants using $A = 2.4 \times 10^{14}$ s^{-1}. The estimated E_a values given in Table 1 correspond to E_a averaged over the temperature range measured. Individual values differed less than 2 kJ·mol^{-1} from the average value presented in Table 1. In some experiments, the pent-4-

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enyl substituent at the benzylic position was replaced by a methyl group. In general, the replacement of the larger alkyl substituent by a methyl group leads to a decrease of the cleavage rate by about 20% (see entries 3 and 4 as well as entries 23 and 24 in Table 1). To better compare the cleavage rates of the various alkoxyamines, rate constants of alkoxyamines with longer alkyl chains were reduced by 20% and the hypothetical rate constants of alkoxyamines with methyl substitution are displayed in Table 1 as k_d^{Me}.

Effect of the *p*-Phenyl Substituent on the Cleavage Rate. It is well-known that *p*-phenyl substitutents affect the reactivity at the benzylic position in various reactions.[18] We therefore studied the effect of the *p*-phenyl substituent on the rate constant of the C−O bond homolysis in TEMPO-styryl derivatives **1a** (*p*-MeO), **1b** (*p*-Me), **1c** (*p*-H), **1e** (*p*-Br), and **1f** (*p*-MeO_2C, Table 1). We can readily see from Table 1 that the reactivity order ($k_{d,OMe} < k_{d,H} \sim k_{d,Me} < k_{d,Br} < k_{d,COOMe}$) correlates neither with the expected reactivity trends for a polar transition state ($k_{d,COOMe}$ ($\sigma_{p,COOMe} = 0.45$) < $k_{d,Br}$ ($\sigma_{p,Br} = 0.23$) < $k_{d,H}$ ($\sigma_{p,H} = 0$) < $k_{d,Me}$ ($\sigma_{p,Me} = -0.17$) < $k_{d,OMe}$ ($\sigma_{p,OMe} = -0.27$))[19] nor with the reactivity order based on the stability of the released benzylic radical ($k_{d,H}$ ($\sigma_{\alpha,H^\bullet} = 0$) < $k_{d,Br}$ ($\sigma_{\alpha,Br^\bullet} \sim 0.012$)[20] < $k_{d,Me}$ ($\sigma_{\alpha,Me^\bullet} = 0.015$) < $k_{d,OMe}$ ($\sigma_{\alpha,OMe^\bullet} = 0.018$) < $k_{d,COOMe}$ ($\sigma_{\alpha,COOMe^\bullet} = 0.043$))[21c] given by the Arnold $\sigma_{\alpha^\bullet}$ scale.[21]

We believe that polar ground-state effects[22] play a role on the activation energy in these alkoxyamine cleavages. The differences in reactivity is probably the result of destabilization of the starting alkoxyamine rather than stabilization of the radical,[23,24] as already suggested by Wayner,[23] Nau[22] and Matyjaszewski[25] for other radical reactions. Polar ground-state effects are weak in our reactions as can be seen from the small slope in Figure 2. Similar results have been presented by Ingold[26a] and Mulder.[26b]

We also studied the cleavage rate in systems where the aryl substituent is replaced by a heteroaryl group. With the 2-pyridyl derivative **1g** a slightly faster homolysis was observed as compared to most of the corresponding non heteroatom containing aryl substituted alkoxyamines (compare entry 7 with entries 1−5 in Table 1). The largest rate constant was obtained for the 2-thienyl derivative **1h** (entry 8). We also included these two values in Figure 2 (Hammet σ_a values for heteroarenes were used in the plot).[27] One can see that both **1g** and especially the thienyl derivative **1h** are out of correlation. However, the increase of k_d upon increasing σ_a is also observed in the heteroaryl series. It is known that σ_a values for heteroarenes are not always reliable, and for **1g** this might explain the deviation from the linearity.[27] However, for the thienyl derivative **1h**, the rate constant is far above the expected value, and so far, we have no explanation for this high rate.

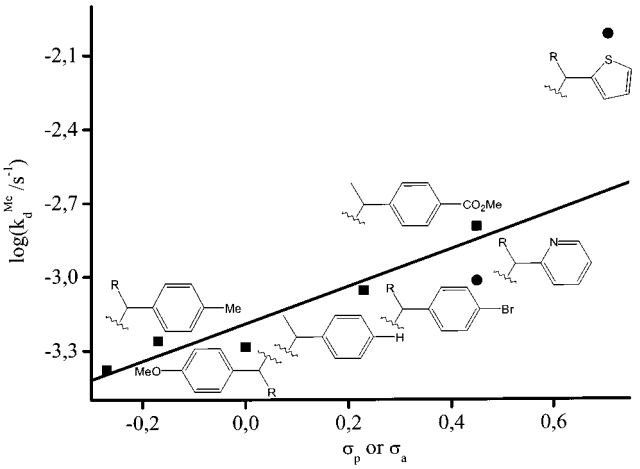

Figure 2. $\log(k_d^{Me})$ for the C−ON bond cleavage in para-subsituted TEMPO−PhEt (square) and TEMPO−$CH(CH_3)$-heteroaryl (circles) derivatives versus Hammett coefficients σ_p[19] and σ_a:[27] $\log(k_d^{Me}/s^{-1}) = -3.20(\pm0.03) + 0.75(\pm0.13)\sigma_p$, $r^2 = 0.92$.

Cleavage Rate Constants of Nonbenzylic Alkoxyamines. We have already studied the effect of the radical stability of the leaving C-radical on the activation energy of the C−O bond homolysis in 13 different TEMPO-derived alkoxyamines.[6] A linear correlation with an r^2 of 0.86 was obtained if E_a was plotted against the C−H bond dissociation energy of the corresponding hydrocarbon ($E_a = -226\ (\pm43) + 0.97(\pm0.12)$BDE(C−H)).[6] Correspondingly, $\log(k_d)$ values at 120 C° obey (eq 3).

$$\log(k_d/s^{-1}) = 38.1(\pm5.6) - 0.11(\pm0.02)\mathrm{BDE(C-H)} \quad (3)$$

To further corroborate this correlation, four additional alkoxyamines bearing nonaromatic substituents at the α position of the alkoxyamine oxygen atom were investigated (Table 1). All these compounds (**1i**−**l**) homolyse slower than the phenyl-substituted TEMPO derivative **1c**. The rate constants were then again correlated with the corresponding C−H BDEs, which were directly obtained from the literature: H−$C(CH_3)_3$ = 404.0(±1.7) kJ mol^{-1};[28] H−$CH(CH_3)CN$ = 375.8(±9.6) kJ mol^{-1};[29] H−$COCH_3$ = 360 kJ mol^{-1};[30] H−$CH(CH_3)SPh$ = 379.0(± 6.1) kJ mol^{-1}.[31]

For nitrile **1l**, k_d is in fair agreement with the value predicted according to Equation 3 (predicted: 5.8×10^{-4}

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(30) Fossey, J.; Lefort, D.; Sorba, J. In *Free Radicals in Organic Chemistry*; Wiley: New York, 1995.
(31) BDE(C−H) was estimated averaging the values from the equations defined by Rüchardt:[33] BDE(C−H) = $1.61a_\alpha^H + 62.4$ (±1.6) and BDE(C−H) = $1.58a_\beta^H + 59.4$ (± 1.3) with $a_\alpha^H = 16.8$ G[34] and $a_\beta^H = 20.76$ G.[34]

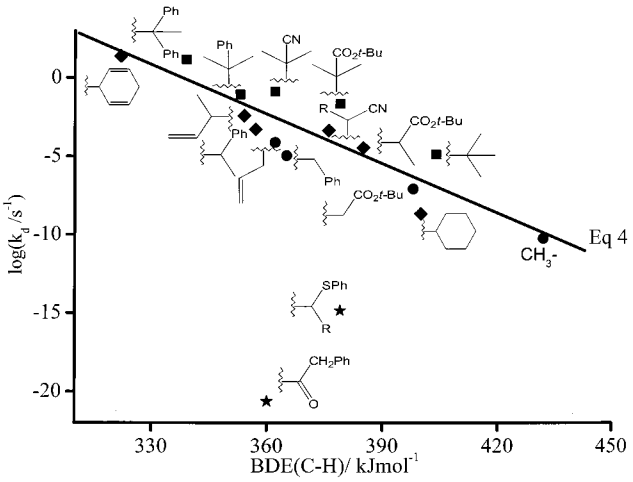

Figure 3. Rate constants log(k_d) for the C−ON bond cleavage of TEMPO derivatives of trialkylhydroxylamines vs BDE-(C−H) of the corresponding hydrocarbon: (■) tertiary alkoxyamines, (♦) secondary alkoxyamines, (●) primary alkoxyamines, (★) other alkoxyamines.

s^{-1}; measured: 3.4×10^{-4} s^{-1}). However, for the tertiary alkoxyamine **1k**, the predicted value is too low (predicted: 4.6×10^{-7} s^{-1}; measured: 1.0×10^{-5} s^{-1}). On the other hand, for the alkoxyamines **1j** (PhS substituent; predicted: 2.6×10^{-4} s^{-1}; measured: 4.1×10^{-8} s^{-1})[32] and **1i** (acyl substituent; predicted: 3.2×10^{-2} s^{-1}; measured: 1.1×10^{-9} s^{-1}) k_d's calculated according to eq 3 are too high. For the tertiary alkoxyamine **1k**, steric relief may account for the lowering of the activation energy. Further, it is not surprising that **1j** does not correlate well with the BDE of the corresponding alkane since Mulder already reported very high E_a's for other α-heteroatom-substituted alkoxyamines (α-alkoxy- as well as for α-ethylaminyl systems),[35] and hyperconjugation probably accounts for the unusual high activation energy in these cases. Thus, in **1j** the oxygen lone pair of the alkoxyamine is delocalized into the σ^* orbital of the C−S-bond, and this may lead to a higher BDE. For the acyl derivative **1i**, the lone pair of the alkoxyamine oxygen can be delocalized into the π^* orbital of the carbonyl group which leads to a partial double bond character for the C−O-TEMPO bond and thus to a very high activation energy for the homolysis, as measured.

In Figure 3 , log(k_d) is plotted against the BDEs of the corresponding alkanes. It includes data from our previous work[6] and **1k** and **1l** but excluding the acyl derivative **1i** and the sulfur **1j**. It leads to eq 4 with $r^2 = 0.80$, which is practically identical to eq 3.

$$\log(k_d/s^{-1}) = 35.5(\pm 5.5) - 0.11(\pm 0.02)\mathrm{BDE(C-H)} \quad (4)$$

One can readily see from Figure 3 that eq 4 can be used to predict rather accurate rate constants for the C−O bond homolysis of TEMPO-alkoxyamines deriving from primary and secondary radicals. For tertiary alkoxyamines, the predicted values are generally too low, probably because of steric effects. However, alkoxyamines with the possibility of stabilization by hyperconjugation are completely out of the correlation.

Solvent Effects and Effect of Camphorsulfonic Acid (CSA) on the Rate Constant of the C−O Bond Homolysis. It is well-known in nitroxide-mediated living radical polymerization that the addition of about 10% CSA leads to increased polymerization rates.[36] Scaiano reported that CSA decreases the rate of the reaction of the benzyl radical with TEMPO by about a factor of 2.[37] However, little is known about the effect of CSA on the rate of the C−O bond rupture.[38] We therefore decided to study the C−O bond homolysis of TEMPO-styryl compound **1c** in the presence of varying amounts of CSA. The rate constant was determined at 130 °C in *tert*-butylbenzene using 10^{-4} M alkoxyamine and 0, 0.25, 0.8, and 1.6 equiv of CSA, respectively. TEMPO is rather stable under these conditions. Thus, in the presence of oxygen with 0.25, 0.8, and 1.6 equiv of TEMPO under the conditions applied in the kinetic experiments, the half-life of TEMPO is above 25 h. In the absence of oxygen, similar results were obtained with 0.25 and 0.8 equiv of CSA. With 1.6 equiv, the half-life of TEMPO is 16 h. In our kinetic experiments, 95% conversion is obtained after 35 min. Thus, a steady-state concentration ($\sim 10^{-4}$ M) of free TEMPO was reached before any significant depletion of TEMPO could have occurred.

It turned out that CSA has no significant effect on the homolysis rate. Without added CSA, a rate constant of 1.6×10^{-3} s^{-1} was measured, and the same rate constant was obtained when the reaction was conducted in the presence of 0.25 and 1.6 equiv of CSA, respectively. A similar rate constant (1.9×10^{-3} s^{-1}, within experimental error) was obtained for the reaction using 0.8 equiv of CSA. We therefore conclude that the effect of CSA in nitroxide-mediated living radical polymerization is mainly to partially remove TEMPO[39] in a rather slow process.

Moad and Rizzardo reported that the rate of the C−O bond homolysis is increasing upon increasing the solvent polarity.[40] We measured the rate of the C−O bond cleavage of alkoxyamine **2c** in the polar solvent system (*t*-butylbenzene/*t*-BuOH = 1:1) and compared the data with previously reported values for the analogous reaction of **2b** in *tert*-butylbenzene. In agreement with the earlier results,[40] the reaction was about two times faster for the polar solvent mixture (**2b**: $k_{(373)}$ (*t*-BuPh) = 1.9×10^{-3} s^{-1}; **2c**: $k_{(373)}^{Me}$ (*t*-BuPh/*t*-BuOH)[41] = 4.0×10^{-3} s^{-1}). Furthermore, the homolysis of **1c** at 120 °C was 2.3 times faster in chlorobenzene than in *tert*-butylbenzene ($k_{(393)}$ (*t*-BuPh) = 5.2×10^{-4} s^{-1}; $k_{(393)}$ (ClPh) = 1.2×10^{-3} s^{-1}). This points to a polar transition state of the homolysis (vide infra). Furthermore, in polar protic solvents inter-

(32) The additional OH group at the nitroxide has only a small effect on the rate of the C−O bond homolysis and can therefore not account for the high activation energy observed: Marque, S.; Fischer, H. Unpublished results.

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(41) A corrected rate constant was used for proper comparison; see the text.

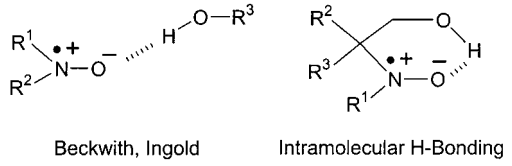

Figure 4. Intramolecular H-bonding.

molecular H-bonding may also accelerate the C−O-bond cleavage.

Intramolecular Hydrogen Bonding. Beckwith and Ingold showed that nitroxides interact with polar protic solvents via intermolecular hydrogen bonding.[42] Recombination rates of various C-centered radicals with TEMPO are affected by the polarity of the solvent with lower rates in polar solvents. H-bonding of the solvent with the nitroxide is responsible for the lowering of the recombination rates (Figure 4).[42] Since the alkoxyamine C−O bond rupture is a rather slow process (late transition state) hydrogen bonding may also influence the rate of the homolysis.[43]

By introducing an appropriately positioned OH group onto the alkoxyamine however (see Figure 4), the polarity of the molecule is altered (polar effect).[40] By considering field effects of the attached substituents we believe that we can distinguish between polar effects and intramolecular H-bonding. Since steric effects also play an important role in these processes,[6] we will only compare data from alkoxyamines for which steric effects should be similar.

Derivative **3a** (entry 16), the corresponding hydroxy compound **6** (entry 20), and the silyloxy derivative **5** (entry 19) all have very similar k_d's for the C−O-bond rupture (Table 1). At first sight, it seems that there is no H-bonding effect on the rate constant. However, the hydroxymethyl group is excerting a much stronger field effect ($\sigma_1 = 0.11$)[44,45] than the silyloxymethyl group ($\sigma_1 \sim 0.00$)[46] and the H-atom ($\sigma_1 = 0.00$). Probably, the stabilization gained by the intramolecular H-bonding in **6** is compensated by the field effect, which in the case of the OH-substituted alkoxyamine **6** strenghtens the C−O bond. Therefore, the methoxy-substituted alkoxyamine **4** ($\sigma_1(CH_3OCH_2) = \sigma_1(HOCH_2)$) was studied.[45] Alkoxyamine **4** was shown to undergo C−O bond rupture about three times slower than the hydroxy derivative **6** (compare entries 18 and 20), thus supporting the occurrence of intramolecular H-bonding in **6**.

Furthermore, alkoxyamine **7a** homolyses about 40 times slower than triol **8a** (compare entries 21 and 23, field effects in **7a** and **8a** should be very similar). Also for the tertiary alkoxyamines **7b** and **8c** the same behavior was observed. Thus, the C−O bond homolysis in the H-bond forming triol **8c** is 66 times faster than in ortho ester **7b** (compare entries 22 and 25). These results can be nicely interpreted in terms of intramolecular H-bonding. To provide additional evidence for the intramolecular H-bonding in these systems we decided to study the free nitroxides by EPR spectroscopy.

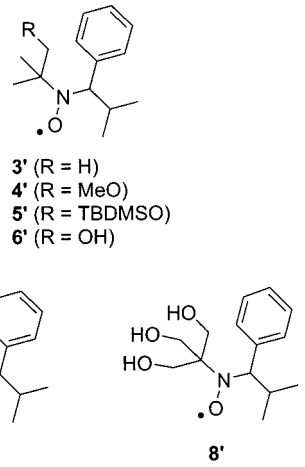

Figure 5. Nitroxides studied by EPR: *N*-(*tert*-butyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl (**3′**), *N*-(1,1-dimethyl-2-methoxypropyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl (**4′**), *N*-(1,1-dimethyl-2-[*tert*-butyldimethylsilanyloxy]propyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl (**5′**), *N*-(1,1-dimethyl-2-hydroxypropyl)-*N*-(2-methyl-1-phenylpropyl)-*N*-oxyl (**6′**), *N*-(2-methyl-1-phenylpropyl)-*N*-(1-methyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl)-*N*-oxyl (**7′**), *N*-(2-methyl-1-phenylpropyl)-*N*-(tris[hydroxymethyl]methyl)-*N*-oxyl (**8′**).

Table 2. EPR Parameters of the New Nitroxides[a]

nitroxide	a_N	a_β^H	g	σ_1[b]
3′	14.83	2.66	2.006	Me, −0.01
4′	14.45	2.76	2.006	CH_2OMe, 0.11
5′	14.76	2.73	2.006	CH_2OSiMe_3, 0.00
6′	14.84	2.72	2.006	CH_2OH, 0.11
7′	13.81	2.72	2.006	*c*
8′	14.88	2.69	2.007	*c*

[a] Hyperfine coupling constants are given in G with an error of ± 0.05 G. [b] σ_1 values are appropriate when the substituent is bonded to a tetrahedral center (i.e., where inductive (throughbond) and field (throughspace) effects are dominant and π-delocalization is minimal). [c] See text.

EPR Hyperfine Coupling Constants. The various nitroxides **3′**-**8′** studied are presented in Figure 5. Hyperfine coupling constants a_N and a_β^H were measured after in situ generation of the nitroxide by thermolysis (120 °C) of deoxygenated solutions of the corresponding alkoxyamine **(4**-**6**, **8a**) in *tert*-butylbenzene.[47] In Table 2 the data of the various new nitroxides are summarized.[48] Furthermore, σ_1-values (field effect) of the various substituents of the nitroxides are also included.[44,45]

Nitroxides have two different resonance structures (see **A** and **B** in Figure 6).[49] Polar solvents as well as hydrogen bonding stabilize structure **B** which leads to an increase of a_N.[45,49,50] Intramolecular H-bonding will also induce a change in the conformation and consequently a change in a_β^H.[45] However, for the nitroxides studied herein,

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(44) Charton, M. In *Progress in Physical Organic Chemistry*; Taft, R. W., Ed.; Wiley: New York, 1987; Vol. 16; p 287. Positive σ_1 values indicate electron-withdrawing substituents whereas negative σ_1's define electron-donating groups, with respect to the H-atom as the internal standard (H: $\sigma_1 = 0$).

(45) Haire, D. L.; Oehler, V. M.; Krygsman, P. H.; Janzen, E. G. *J. Org. Chem.* **1988**, *53*, 4535.

(46) σ_1-value for $Me_3SiOCH_2 = 0.00$.[19] We assume that the TBDMSOCH$_2$ group induces as similar field effect than the Me_3SiOCH_2 group.

(47) This in situ nitroxide generation is very useful for obtaining EPR data of rather unstable nitroxides.

(48) EPR parameters of **3′**, generated by reacting isopropyl radicals with phenyl *N*-*tert*-butyl nitrone, have already been reported, and are in good agreement with our data. Maillard, Ph.; Massot, J. C.; Giannotti, C. *J. Organomet. Chem.* **1978**, *159*, 219.

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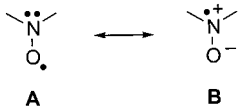

A **B**

Figure 6. Two resonance structures of a nitroxide.

hydrogen bonding will not lock the conformation around N−C_β, and therefore no change of a_β^H is occurring (Table 2). No significant differences of a_N exists between **3′** (a_N = 14.83 G), **5′** (a_N = 14.76 G), and **6′** (a_N = 14.84 G). This result does not necessarily exclude the occurrence of intramolecular H-bonding in **6′** since Janzen pointed out, that electron-withdrawing substituents (field effect, positive σ_1 value) will stabilize structure **A**[45] and in turn lead to a smaller a_N hyperfine coupling constant. We believe that the H-bonding effect in **6′** is compensated by the field effect. To clarify this point, we also studied the methyl ether **4′**, where H-bonding is impossible and the field effect is very similar to the corresponding value in **6′**. Indeed, a much smaller a_N value (14.45) was measured as compared to **6′** (a_N = 14.84 G). This supports our assumption of the formation of an intramolecular H-bond in nitroxides of this type.

We also studied the EPR data of **8′** and compared the value with the corresponding protected, non-H-bond-forming nitroxide **7′**. In agreement with the formation of an intramolecular H-bond in **8′**, a much higher a_N value (14.88) was obtained than for the non-H-bond-forming nitroxide **7′** (a_N = 13.81 G). These results support that the rate accelerations of the C−O-bond cleavage in alkoxyamines capable of intramolecular H-bonding (late transition state with high nitroxide character) reported in the previous section, are probably caused by the interaction of the HO groups with the nitroxide oxygen atom.

Conclusions

In this work, we report the synthesis and the kinetics of the C−O bond cleavage of various new alkoxyamines. We present homolysis rate constants in a series of para-substituted TEMPO-styryl compounds: TEMPO-CH-(CH_3)C_6H_5X (**1a** (*p*-MeO), **1b** (*p*-Me), **1d** (*p*-H), **1e** (*p*-Br), and **1f** (*p*-MeO_2C, Table 1)). The reactivity order **1f** (*p*-MeO_2C) > **1e** (*p*-Br) > **1d** (*p*-H) > **1b** (*p*-Me) > **1a** (*p*-MeO) can be understood by assuming a polar ground-state effect.[22] Furthermore, rate constants for the C−O bond cleavage of α-heteroaryl-substituted secondary alkoxyamines are discussed. It turned out, that by replacing the phenyl group of the TEMPO-styryl derivative **1c** by a heteroaryl group (→ **1g** (2-pyridyl), **1h** (2-thienyl)) a higher reactivity of the modified alkoxyamine is observed.

These results are especially important for nitroxide-mediated living free radical polymerizations. A fast C−O bond cleavage of the alkoxyamine (the initator or the "dormant" polymer, respectively) leads to an efficient polymerization.[4] Thus, vinylstyrenes bearing electron-withdrawing substituents at the para position (π-acceptors) such as *p*-alkoxycarbonylphenylstyrene or *p*-cyanophenylstyrene should be readily polymerized by TEMPO-mediated polymerizations.[51] In addition, heteroaryl-substituted vinyl compounds are predicted to be suitable monomers for nitroxide-mediated living free radical polymerization.[52]

Furthermore, we suggest a correlation by which rate constants for the C−O bond cleavage of TEMPO-derived alkoxyamines can be predicted from the C−H BDEs of the corresponding alkanes. Moreover, we show that the addition of CSA, which is often used as an additive in polymerization,[36] has no effect on the rate of the C−O bond rupture in TEMPO-styryl alkoxyamine **1c**. Polar solvents are shown to increase the rate of the bond homolysis.

Finally, we present EPR and kinetic evidence that alkoxyamines derived from nitroxides which are capable of intramolecular H-bonding undergo C−O bond cleavage faster than the corresponding non-H-bond-forming analogues. The concept of intramolecular H-bonding is very important for the design of new alkoxyamines for which the bond homolysis should occur under much milder conditions. Experiments along this line are underway.

Experimental Section

General Methods. All reactions were carried out in oven-dried glassware under an argon atmosphere. Tetrahydrofuran (THF) and benzene (PhH) were freshly distilled from sodium/benzophenone under argon. Melting points are uncorrected. IR spectra were recorded using an FTIR apparatus. Mass spectra were obtained by EI, ESI, or MALDI methods. Flash column chromatography was performed using Fluka silica gel *60* (40−63 μm). Elemental analyses were performed by the Microanalytical Laboratory of the Laboratorium für Organische Chemie, ETH-Zürich. Experimental setup for the kinetic EPR experiments has previously been described.[6]

General Procedure (GP 1) for the Preparation of the Alkoxyamines via Nucleophilic Substitution. To a suspension of TEMPO in H_2O was added calcium L-ascorbate dihydrate. The suspension was stirred at rt for 10−15 min until all of the TEMPO was consumed. The reaction mixture was then extracted twice with Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated to afford 1-hydroxy-2,2,6,6-tetramethylpiperidine. The 1-hydroxy-2,2,6,6-tetramethylpiperidine was dissolved under Ar in THF and added to a suspension of NaH in THF at rt. After the mixture was stirred for 30 min, a solution of the bromide or mesylate in THF was added. The resulting reaction mixture was heated to reflux and stirred for 10−20 h. H_2O was added, and the mixture was extracted twice with Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated. Purification by FC afforded the pure alkoxyamine.

General Procedure (GP 2) for the Preparation of the Alkoxyamines via the Matyiaszewski Method.[12] The benzylic bromide, nitroxide, Cu powder, $Cu(OTf)_2$, and 4,4′-di-*tert*-butyl-2,2′-bipyridyl were suspended under Ar in benzene (sealed tube). The reaction mixture was stirred at 65−70 °C for 6−20 h. The solids were then removed by filtration (washing with Et_2O). Purification by FC afforded the pure alkoxyamine.

2,2,6,6-Tetramethyl-1-(1-(4-methoxyphenyl)hex-5-enoyloxy)piperidine (1a). According to GP1 with TEMPO (344 mg, 2.20 mmol), H_2O (15 mL), Ca-ascorbate (864 mg, 2.20 mmol), 1-bromo-1-(4-methoxyphenyl)-5-hexene (250 mg, 0.93 mmol) in THF (1 mL), NaH (92 mg, 60%, 2.30 mmol) in THF (3 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:100) afforded **1a**, 74 mg (23%). IR ($CHCl_3$): 3005 w, 2934 s, 1610 m, 1512 s,

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1463 m, 1035 m, 914 m, 833 s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.19 (d, $J = 8.6$ Hz, 2 H), 6.83 (d, $J = 8.6$ Hz, 2 H), 5.77−5.67 (m, 1 H), 4.96−4.87 (m, 2 H), 4.52 (dd, $J_1 = 4.1$ Hz, $J_2 = 10.0$ Hz, 1 H, HCO), 3.80 (s, 3 H, OCH_3), 2.12−1.91 (m, 3 H), 1.80−1.70 (m, 1 H), 1.60−0.90 (m, 18 H), 0.52 (s, br, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.6, 138.9, 136.0, 128.9, 114.3, 113.1, 86.7, 60.0, 59.3, 55.2, 40.4, 35.3, 34.2, 33.8, 25.0, 20.3, 17.2. EI-MS: 189.1 (71), 147.1 (43), 121.0 (100). Anal. Calcd for $C_{22}H_{35}NO_2$ (345.52): C, 76.48; H, 10.21; N, 4.05. Found: C, 76.59; H, 10.17; N, 3.86.

2,2,6,6-Tetramethyl-1-(1-tolylhex-5-enoyloxy)piperidine (1b). According to GP2 with 1-bromo-1-tolyl-5-hexene (293 mg, 1.16 mmol), TEMPO (357 mg, 1.39 mmol), Cu (78 mg, 1.22 mmol), $Cu(OTf)_2$ (4.2 mg, 12 μmol), and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (13 mg, 0.046 mmol) in benzene (1.74 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:150) afforded **1b**, 95 mg (25%). IR ($CHCl_3$): 2933 s, 1514 m, 1360 m, 1132 m, 972 m, 914 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.20−7.00 (m, 5 H), 5.76−5.66 (m, 1 H), 4.95−4.86 (m, 2), 4.54 (dd, $J_1 = 9.8$ Hz, $J_2 = 4.0$ Hz, 1 H, HCO), 2.33 (s, 3 H, CH_3), 2.12−1.90 (m, 3 H), 1.85−1.75 (m, 1 H), 1.60−1.06 (m, 14 H), 0.99 (s, br, 3 H, CH_3); 0.56 (s, br, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7, 138.9, 136.4, 128.5, 127.7, 114.3, 87.1, 60.0, 40.5, 35.4, 34.3, 33.8, 24.8, 21.2, 20.3, 17.2. EI-MS: 329.2 (<1, $[M]^+$), 173.1 (13, $[M - TEMPO]^+$), 105.0 (100).

2,2,6,6-Tetramethyl-1-(1-phenylhex-5-enoyloxy)piperidine (1d). According to GP1 with TEMPO (438 mg, 2.80 mmol), H_2O (10 mL), Ca-ascorbate (1.194 g, 2.80 mmol), 1-bromo-1-phenyl-5-hexene (300 mg, 1.28 mmol) in THF (1 mL), NaH (112 mg, 60%, 2.80 mmol) in THF (5 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:130) afforded **1d**, 314 mg (80%). IR ($CHCl_3$): 3007 s, 2932 s, 2870 s, 1639 m, 1454 s, 1376 s, 1361 s, 1257 m, 1133 s, 972 s, 915 s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.30−7.20 (m, 5 H), 5.76−5.67 (m, 1 H), 4.95−4.87 (m, 2), 4.57 (dd, $J_1 = 9.8$ Hz, $J_2 = 4.0$ Hz, 1 H, HCO), 2.12−1.90 (m, 3 H), 1.85−1.75 (m, 1 H), 1.60−1.06 (m, 14 H), 0.99 (s, br, 3 H, CH_3), 0.53 (s, br, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.8, 138.8, 127.8, 126.9, 114.4, 87.4, 59.4, 40.5, 35.4, 34.3, 34.1, 33.8, 24.7, 20.3, 17.2. EI-MS: 316.3 (<1, $[M + 1]^+$), 142.1 (100). Anal. Calcd for $C_{21}H_{33}NO$ (315.50): C, 79.95; H, 10.54; N, 4.44. Found: C, 79.96; H, 10.81; N, 4.49.

2,2,6,6-Tetramethyl-1-(1-(4-bromophenyl)hex-5-enoyloxy)piperidine (1e). According to GP1 with TEMPO (313 mg, 2.00 mmol), H_2O (10 mL), Ca-ascorbate (785 mg, 2.00 mmol), 1-bromo-1-(4-bromophenyl)-5-hexene (580 mg, 1.82 mmol) in THF (1 mL), NaH (88 mg, 60%, 2.20 mmol) in THF (3 mL) for 20 h. Purification by FC (Et_2O/pentane = 1:100) afforded **1e**, 338 mg (47%). IR ($CHCl_3$): 2934 s, 2870 w, 1639 w, 1485 m, 1376 m, 1361 m, 1132 m, 1071 m, 915 m, 828 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.42 (d, $J = 8.4$ Hz, 2 H), 7.15 (d, $J = 8.3$ Hz, 2 H), 5.75−5.65 (m, 1 H), 4.96−4.88 (m, 2 H), 4.54 (dd, $J_1 = 4.0$ Hz, $J_2 = 9.8$ Hz, 1 H, HCO), 2.09−1.90 (m, 3 H), 1.79−1.71 (m, 1 H), 1.50−0.90 (m, 17 H), 0.52 (s, br, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 138.6, 131.0, 129.5, 120.7, 114.6, 86.7, 60.0, 59.5, 40.4, 35.3, 34.3, 33.7, 24.6, 20.3, 17.2. EI-MS: 378.2 (<1, $[M - CH_3]^+$), 142.2 (100). Anal. Calcd for $C_{21}H_{32}NOBr$ (394.39): C, 63.95; H, 8.18; N, 3.55. Found: C, 64.16; H, 8.22; N, 3.34.

4-[1-(2,2,6,6-Tetramethylpiperidin-1-yloxy)ethyl]benzoic Acid Methyl Ester (1f). According to GP2 with 4-(1-bromoethyl)benzoic acid methyl ester (338 mg, 1.39 mmol), TEMPO (426 mg, 1.66 mmol), Cu (93 mg, 1.46 mmol), $Cu(OTf)_2$ (4.9 mg, 0.014 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (15.5 mg, 0.055 mmol) in benzene (2.1 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:20) afforded **1f**, 110 mg (25%). Mp: 88−89 °C. IR ($CHCl_3$): 2933 m, 1718 s, 1282 s cm^{-1}. ^1H NMR (400 MHz): δ 7.98 (d, $J = 8.4$ Hz, 2 H), 7.38 (d, $J = 8.1$ Hz, 2 H), 4.82 (q, $J = 6.7$ Hz, 1 H, HCO), 3.91 (s, 3 H, OCH_3), 1.48 (d, $J = 6.7$ Hz, 3 H, CH_3), 1.60−1.20 (m, 6 H), 1.29 (s, br, 3 H, CH_3), 1.17 (s, br, 3 H, CH_3), 1.02 (s, br, 3 H, CH_3), 0.62 (s, br, 3 H, CH_3).^{13}C NMR (100 MHz): δ 167.2, 151.2, 129.5, 126.5, 83.0, 59.7, 52.0, 40.4, 34.2, 23.6, 20.3, 17.2. ESI-MS: 319.2 (<1, $[M]^+$), 156.1 (100). Anal. Calcd for $C_{19}H_{29}NO_3$ (319.44): C, 71.44; H, 9.15; N, 4.38. Found: C, 71.38; H, 9.26; N, 4.35.

2,2,6,6-Tetramethyl-1-(1-(2-pyridyl)hex-5-enoyloxy)-piperidine (1g). According to GP1 with TEMPO (868 mg, 5.56 mmol), H_2O (37 mL), Ca-ascorbate (2.19 g, 5.56 mmol), 1-mesyloxy-1-(2-pyridyl)-5-hexene (670 mg, 2.78 mmol) in THF (2 mL), NaH (222 mg, 60%, 5.56 mmol) in THF (9 mL) for 15 h. Purification by FC (Et_2O/pentane = 1:7) afforded **1g**, 214 mg (24%). IR ($CHCl_3$): 2935 s, 1639 w, 1592 m, 1434 m, 1361 m, 1133 m, 914 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 8.57−8.52 (m, 1 H), 7.66−7.62 (m, 1 H), 7.38−7.35 (m, 1 H), 7.16−7.12 (m, 1 H), 5.76−5.66 (m, 1 H), 4.96−4.86 (m, 2 H), 4.76 (dd, $J_1 = 4.2$ Hz, $J_2 = 9.4$ Hz, 1 H, HCO), 2.15−1.92 (m, 4 H), 1.60−1.10 (m, 17 H), 1.01 (s, 3 H, CH_3), 0.43 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.0, 148.7, 138.7, 135.8, 123.0, 122.0, 114.4, 88.1, 60.1, 59.3, 40.4, 34.2, 33.7, 24.6, 20.3, 17.2. EI-MS: 317.2 (2, $[M + 1]^+$), 160.0 (100). Anal. Calcd for $C_{20}H_{32}N_2O$ (316.49): C, 75.90; H, 10.19; N, 8.85. Found: C, 75.97; H, 9.97; N, 8.84.

2,2,6,6-Tetramethyl-1-(1-(2-thienyl)hex-5-enoyloxy)-piperidine (1h). According to GP1 with TEMPO (1.12 g, 7.20 mmol), H_2O (48 mL), Ca-ascorbate (2.84 g, 7.20 mmol), 1-bromo-1-(2-thienyl)-5-hexene (960 mg, 3.57 mmol) in THF (3 mL), NaH (287 mg, 60%, 7.20 mmol) in THF (10 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:100 → 1:10) afforded **1h**, 306 mg (27%). IR ($CHCl_3$): 2933 s, 1639 m, 1461 m, 1376 m, 1361 m, 1132 m, 915 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.23−7.21 (m, 1 H), 6.94−6.91 (m, 2 H), 5.80−5.70 (m, 1 H), 5.00−4.90 (m, 2 H), 4.85 (dd, $J_1 = 4.5$ Hz, $J_2 = 9.6$ Hz, 1 H, HCO), 2.19−1.96 (m, 3 H), 1.85−1.76 (m, 1 H), 1.60−1.20 (m, 11 H), 1.15 (s, 3 H, CH_3), 1.01 (s, 3 H, CH_3), 0.61 (s, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 138.7, 125.9, 125.6, 124.4, 114.5, 82.0, 60.2, 59.5, 40.4, 35.8, 34.3, 33.6, 33.0, 25.2, 20.4, 17.2. EI-MS: 165.1 (52, $[M - TEMPO]^+$), 123.1 (79), 97.1 (100). Anal. Calcd for $C_{19}H_{31}NOS$ (321.53): C, 70.98; H, 9.72; N, 4.36. Found: C, 70.92; H, 9.71; N, 4.25.

Phenylacetic Acid 2,2,6,6-Tetramethylpiperidin-1-yl Ester (1i). To a supension of TEMPO (1.16 g, 7.44 mmol) in H_2O (50 mL) was added calcium L-ascorbate dihydrate (2.93 g, 7.44 mmol). The suspension was stirred at rt until all of the TEMPO was consumed. The reaction mixture was then extracted twice with Et_2O. The combined organic phases were dried ($MgSO_4$) and evaporated to afford 1-hydroxy-2,2,6,6-tetramethylpiperidine. The 1-hydroxy-2,2,6,6-tetramethylpiperidine was dissolved under Ar in THF (2 mL) and added to a suspension of NaH (298 mg, 7.44 mmol) in THF (10 mL) at rt. After the mixture was stirred for 30 min, a solution of phenylacetyl chloride (0.99 mL, 7.44 mmol) was added followed by a catalytic amount of (dimethylamino)pyridine. The resulting reaction mixture was stirred at rt for 15 h. Saturated aqueous NH_4Cl solution was added, and the mixture was extracted twice with Et_2O. After the mixture was washed with brine, the combined organic phases were dried ($MgSO_4$) and evaporated. Purification by FC (Et_2O/pentane = 1:5) afforded **1i**, 1.84 g (89%). IR ($CHCl_3$): 2980 s, 2941 s, 1752 s, 1117 s, 936 m cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.36−7.24 (m, 5 H), 3.66 (s, 2 H), 1.69−1.36 (m, 6 H), 1.04 (s, 6 H, 2 CH_3), 0.94 (s, 6 H, 2 CH_3), 1.16 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.09 (s, 6 H, 2 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 134.1, 129.4, 128.5, 127.0, 60.1, 40.6, 39.0, 31.7, 20.4, 16.9. EI-MS: 275.2 (1, $[M + 1]^+$), 126.2 (100).

4-Hydroxy-2,2,6,6-tetramethyl-1-((1-phenylsulfanyl)-hex-5-enoyloxy)piperidine (1j). According to GP1 with 4-TBDMSO-TEMPO (2.29 g, 8.0 mmol), H_2O (14 mL)/MeOH (27 mL), Ca-ascorbate (3.49 g, 8.20 mmol), 1-chloro-1-phenylsulfanyl-5-hexene (1.18 g, 5.21 mmol) in THF (2 mL), NaH (328 mg, 60%, 8.20 mmol) in THF (7 mL) for 16 h. Purification by FC (Et_2O/pentane = 1:100) afforded TBDMS-potected **1j**, 532 mg (21%). TBDMS-protected **1j** (530 mg) was dissolved in THF (14 mL). TBAF·$(H_2O)_3$ (868 mg, 2.75 mmol) was added and the resulting solution stirred at rt for 3.5 h. After addition of Et_2O, the reaction mixture was washed with aqueous NH_4-Cl and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by FC (Et_2O/pentane = 1:1) afforded **1j**, 170 mg (43%). IR ($CHCl_3$): 3603 s, 3442 m br, 2940 s, 1478 s, 1378 s, 1365 s, 1045 s, 1026 s, 998 s, 955 s, 916 s cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.61−7.57 (m, 2 H), 7.31−7.19 (m, 3 H), 5.80−5.70 (m, 1 H), 5.19 (dd, $J_1 = 3.9$ Hz, $J_2 = 9.0$ Hz,

1 H, HCO), 5.00−4.91 (m, 2 H), 3.98−3.95 (m, 1 H), 2.20−2.10 (m, 3 H), 1.90−1.40 (m, 7 H), 1.34 (s, 3 H, CH_3), 1.21 (s, 3 H, CH_3), 1.16 (s, 6 H, $2CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.5, 135.6, 132.2, 128.6, 126.7, 114.7, 94.0, 63.2, 61.0, 60.3, 48.9, 48.7, 34.7, 34.01, 33.96, 33.4, 25.5, 21.64, 21.55. EI-MS: 191.1 (20, [M − TEMPO − OH]$^+$), 110.1 (100). Anal. Calcd for $C_{21}H_{33}NO_2S$ (363.56): C, 69.38; H, 9.15; N, 3.85. Found: C, 69.41; H, 9.30; N, 3.79.

1-(1,1-Dimethylhex-5-enyloxy)-2,2,6,6-tetramethylpiperidine (1k). 6-Iodo-6-methyl-1-heptene (238 mg, 1.0 mmol) and TEMPO (468 mg, 3.0 mmol) were dissolved under Ar in benzene (10 mL) and heated to reflux. Bu_3SnH (0.54 mL, 2.0 mmol) was added in three portions in 60 min intervals. After complete addition, stirring was continued for 30 min. Removal of the solvent and purification by FC (Et_2O/pentane = 1:150) afforded **1k**, 63 mg (24%). IR ($CHCl_3$): 2973 s, 2935 s, 1468 m, 1375 s, 1361 s, 1132 s, 916 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89−5.78 (m, 1 H), 5.04−4.92 (m, 2 H), 2.07−2.01 (m, 2 H), 1.65−1.40 (m, 12 H), 1.24 (s, 6 H, 2 CH_3), 1.10 (s, 6 H, 2 CH_3), 1.07 (s, 6 H, 2 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.3, 114.2, 78.6, 59.2, 43.1, 40.9, 34.8, 34.5, 26.9, 23.7, 20.7, 17.2. EI-MS: 268.3 (<1, [M + 1]$^+$), 142.1 (100). Anal. Calcd for $C_{17}H_{33}NO$ (267.45): C, 76.34; H, 12.44; N, 5.24. Found: C, 76.37; H, 12.37; N, 5.24.

2-(2,2,6,6-Tetramethylpiperidin-1-yloxy)hept-6-enenitrile (1l). A solution of hept-6-enenitrile (300 mg, 2.75 mmol) in THF (2 mL) was added at −78 °C to an LDA solution (2.90 mmol) in THF (6 mL). Stirring was continued at −78 °C for 90 min. A suspension of TEMPO (455 mg, 2.90 mmol) and $CuCl_2$ (389 mg, 2.90 mmol) in THF (10 mL) was added, and the resulting reaction mixture was allowed to warm to rt overnight. Saturated aqueous NH_4Cl solution was added, and the biphasic mixture was extracted with Et_2O (three times). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Purification by FC (Et_2O/pentane = 1:20) afforded **1l**: 485 mg (67%). IR ($CHCl_3$): 2936 s, 2872 m, 1461 m, 1378 m, 1364 m, 1132 s, 992 m, 918 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.99−5.75 (m, 1 H), 5.08−4.99 (m, 2 H), 4.62 (dd, J_1 = 5.8 Hz, J_2 = 7.1 Hz, 1 H, HCO), 2.15−2.10 (m, 2 H), 1.95−1.80 (m, 2 H), 1.80−1.40 (m, 8 H), 1.34 (s, 3 H, CH_3), 1.16 (s, 3 H, CH_3), 1.11 (s, 3 H, CH_3), 1.09 (s, 6 H, 2 CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.7, 119.7, 115.4, 74.1, 60.9, 59.9, 40.0, 39.9, 34.1, 33.7, 33.2, 32.3, 24.0, 20.4, 20.3, 17.0. EI-MS: 265.2 (1, [M + 1]$^+$), 156.1 (100). Anal. Calcd for $C_{16}H_{28}N_2O$ (264.41): C, 72.68; H, 10.67; N, 10.59. Found: C, 72.84; H, 10.36; N, 10.46.

***N,N*-Di-*tert*-butyl-*O*-(1,1-dimethylhex-5-enyl)hydroxylamine (2a).** 6-Iodo-6-methyl-1-heptene (500 mg, 2.10 mmol) and *N*,*N*-di-*tert*-butyl nitroxide (756 mg, 5.25 mmol) were dissolved under Ar in benzene (20 mL) and heated to reflux. Bu_3SnH (1.02 mL, 3.78 mmol) was added in three portions in 60 min intervals. After complete addition, stirring was continued for 30 min. Removal of the solvent and purification by FC (Et_2O/pentane = 1:150) afforded **2a**, 252 mg (47%). IR ($CHCl_3$): 2973 s, 1384 s, 1362 s, 1178 w, 914 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.88−5.76 (m, 1 H), 5.03−4.91 (m, 2 H), 2.06−2.00 (m, 2 H), 1.64−1.45 (m, 4 H), 1.25 (s, 6 H, 2 CH_3), 1.21 (s, 18 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.2, 114.2, 79.5, 60.9, 42.8, 34.5, 31.0, 27.0, 23.6. ESI-MS: 256.4 (100, [M + 1]$^+$).

***N,N*-Di-*tert*-butyl-*O*-(1-phenylhex-5-enyl)hydroxylamine (2c).** According to GP1 with *N*,*N*-di-*tert*-butyl nitroxide (403 mg, 2.80 mmol), H_2O (10 mL), Ca-ascorbate (1.194 g, 2.80 mmol), 1-bromo-1-phenyl-5-hexene (300 mg, 1.28 mmol) in THF (1 mL), NaH (112 mg, 60%, 2.80 mmol) in THF (5 mL) for 44 h. Purification by FC (Et_2O/pentane = 1:120) afforded **2c**, 185 mg (24%). IR ($CHCl_3$): 2971 s, 2931 s, 1494 m, 1453 m, 1386 m, 1362 s, 976 m, 912 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35−7.20 (m, 5 H), 5.76−5.66 (m, 1 H), 4.96−4.87 (m, 2 H), 4.60 (dd, J_1 = 3.9 Hz, J_2 = 10.3 Hz, 1 H, HCO), 2.21−2.12 (m, 1 H), 2.07−1.91 (m, 2 H), 1.83−1.73 (m, 1 H), 1.31 (s, 9 H, *t*-Bu), 1.20−1.00 (m, 2 H), 0.97 (s, 9 H, *t*-Bu). ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 138.8, 128.3, 127.8, 127.1, 114.4, 87.4, 62.1, 61.7, 34.5, 33.8, 30.7, 30.6, 25.1. FAB-MS: 304.3 (25, [M + 1]$^+$), 145.2 (100). Anal. Calcd for $C_{20}H_{33}NO$ (303.49): C, 79.15; H, 10.96; N, 4.62. Found: C, 79.24; H, 11.02; N, 4.51.

***N*-*tert*-Butyl-*N*-(2-methyl-1-phenylpropyl)-*O*-(1-phenylhex-5-enyl)hydroxylamine (3a).** According to GP2 with 1-bromo-1-phenyl-5-hexene (478 mg, 2.00 mmol), TIPNO[13b] (469 mg, 2.13 mmol), Cu (135 mg, 2.11 mmol), $Cu(OTf)_2$ (7 mg, 20 μmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (22 mg, 0.08 mmol) in benzene (4.0 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:120) afforded **3a** as mixture of diastereoisomers (∼1:1), 236 mg (31%). ^{1}H NMR (400 MHz): isomer A, δ 7.50−7.10 (m, 10 H), 5.79−5.66 (m, 1 H), 4.99−4.88 (m, 2 H), 4.73 (dd, J_1 = 3.7 Hz, J_2 = 10.0 Hz, 1 H, PhC*H*O), 3.41 (d, J = 10.6 Hz, 1 H, *i*PrC*H*Ph), 2.40−2.15 (m, 2 H), 2.15−1.70 (m, 3 H), 1.30 (d, J = 6.4 Hz, 3 H, CH_3), 1.30−1.10 (m, 2 H), 0.73 (s, 9 H, *t*Bu), 0.55 (d, J = 6.6 Hz, 3 H); isomer B, δ 7.50−7.10 (m, 10 H), 5.79−5.66 (m, 1 H), 4.99−4.88 (m, 2 H), 4.63 (dd, J_1 = 4.1 Hz, J_2 = 10.8 Hz, 1 H, PhC*H*O), 3.24 (d, J = 10.7 Hz, 1 H, *i*PrC*H*Ph), 2.40−2.15 (m, 2 H), 2.15−1.70 (m, 3 H), 1.30−1.10 (m, 2 H), 1.04 (s, 9 H, *t*Bu), 0.80 (d, J = 6.3 Hz, 3 H, CH_3), 0.17 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz): isomer A, δ 143.4, 142.6, 138.7, 130.8, 127.9, 127.5, 127.4, 127.4, 126.8, 126.3, 114.6, 87.7, 72.5, 60.2, 36.1, 33.7, 32.0, 28.3, 24.7, 22.1, 21.2; isomer B, δ 143.2, 142.3, 138.7, 130.9, 128.2, 127.9, 127.6, 127.2, 126.1, 114.5, 87.7, 72.0, 60.8, 35.4, 33.7, 31.3, 28.4, 25.3, 22.1, 20.9. FAB-MS: 380.3 (29, [M + H]$^+$), 178.2 (100). Anal. Calcd for $C_{26}H_{37}NO$ (379.58): C, 82.27; H, 9.82; N, 3.69. Found: C, 82.05; H, 9.70; N, 3.66.

***N*-[1,1-Dimethylethyl-2-(methoxy)]-*N*-(2-methyl-1-phenylpropyl-*O*-(1-phenylethyl)hydroxylamine (4).** According to GP2 with (1-bromoethyl)benzene (0.41 mL, 3.0 mmol), TBDMSTIPNO[13b] (1.12 g, 3.20 mmol), Cu (202 mg, 3.16 mmol), $Cu(OTf)_2$ (10.6 mg, 0.03 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (33 mg, 0.12 mmol) in benzene (6.0 mL) for 12 h. Purification by FC (Et_2O/pentane = 1:150) afforded TBDMS-**4** as mixture of diastereoisomers (∼1.5:1): 875 mg (64%). Desilylation according to the preparation of **6** with TBAF·$(H_2O)_3$ (1.21 g, 3.84 mmol) in THF (60 mL) afforded after purification by FC (Et_2O/pentane = 1:10) HO-**4** (546 mg, 83%). A solution of the hydroxy compound HO-**4** (300 mg, 0.88 mmol) in THF (2 mL) was added at rt to a suspension of NaH (54 mg, 1.32 mmol) in THF (10 mL). After stirring for 30 min at rt, MeI (0.17 mL, 2.64 mmol) was added and the resulting mixture was heated to reflux for 7 h. Saturated aqueous NH_4Cl was added, and the biphasic mixture was extracted three times with Et_2O. The combined organic phases were additionally washed with brine and dried ($MgSO_4$). Evaporation of the solvents and purification by FC (Et_2O/pentane = 1:100) afforded **4**, 195 mg (62%). IR ($CHCl_3$): 2980 s, 1451 m, 1104 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): both isomers δ 7.51−7.15 (m, 10 H), 4.95−4.88 (m, 1 H, HC(Ph)O), 3.45 (d, J = 10.6 Hz, 1 H, CHO, isomer A), 3.32 (d, J = 10.3 Hz, 1 H, CHO, A), 3.30 (s, 3 H, OCH_3, A), 3.15−3.12 (m, 1 H, NCH, B), 2.99 (s, 3 H, OCH_3, B), 2.86 (d, J = 9.1 Hz, 1 H, CHO, B), 2.64 (d, J = 9.1 Hz, 1 H, CHO, B), 2.39−2.28 (m, 1 H), 1.63 (d, J = 6.7 Hz, 3 H, CH_3, B), 1.55 (d, J = 6.6 Hz, 3 H, CH_3, A), 1.32 (d, J = 6.4 Hz, 3 H, CH_3, B), 1.12 (s, 3 H, CH_3, A), 0.95 (s, 3 H, CH_3, B), 0.93 (d, J = 6.3 Hz, 3 H, CH_3, A), 0.90 (s, 3 H, CH_3, A), 0.59 (s, 3 H, CH_3, B), 0.54 (d, J = 6.6 Hz, 3 H, CH_3, B), 0.22 (d, J = 6.6 Hz, 3 H, CH_3, B). ^{13}C NMR (100 MHz, $CDCl_3$): isomer A, δ 144.8, 142.2, 127.3, 127.2, 127.0, 126.8, 126.4, 126.3, 82.6, 80.1, 72.0, 63.6, 59.0, 31.7, 29.6, 23.8, 23.0, 22.3, 22.1, 21.1; isomer B, δ = 145.7, 142.5, 130.9, 128.14, 128.07, 127.4, 126.3, 83.3, 80.2, 72.1, 63.2, 58.7, 32.0, 24.6, 23.7, 22.0, 21.3, 21.2. Anal. Calcd for $C_{23}H_{33}NO_2$ (355.52): C, 77.70; H, 9.36; N, 3.94. Found: C, 77.63; H, 9.19; N, 3.73.

***N*-[2-(*tert*-Butyldimethylsilanyloxy)-1,1-dimethylethyl]-*N*-(2-methyl-1-phenylpropyl-*O*-(1-phenylhept-6-enyl)hydroxylamine (5).** According to GP2 with 1-bromo-1-phenyl-6-heptene (359 mg, 1.50 mmol), TBDMSTIPNO[13b] (560 mg, 1.60 mmol), Cu (101 mg, 1.58 mmol), $Cu(OTf)_2$ (5.3 mg, 15 μmol), and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (16.5 mg, 0.06 mmol) in benzene (3.0 mL) for 22 h. Purification by FC (Et_2O/pentane = 1:150) afforded **5** as mixture of diastereoisomers (∼2:1): 605 mg (79%). IR ($CHCl_3$): 2929 s, 2857 m, 1471 m, 1098 s, 913 m, 838 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): both isomers, δ

7.52−7.14 (m, 5 H), 5.81−5.68 (m, 1 H), 4.98−4.87 (m, 2 H), 4.74 (dd, J_1 = 3.7 Hz, J_2 = 10.1 Hz, 1 H, HCO, major), 4.64 (dd, J_1 = 4.0 Hz, J_2 = 11.1 Hz, 1 H, HCO, minor), 3.55 (d, J = 9.5 Hz, 1 H, H−COSi, minor), 3.47 (d, J = 10.6 Hz, 1 H, PhCHN, major), 3.34 (d, J = 9.5 Hz, 1 H, H−COSi, minor), 3.28 (d, J = 10.8 Hz, 1 H, PhCHN, minor), 2.98 (d, J = 9.5 Hz, 1 H, H−COSi, major), 2.87 (d, J = 9.5 Hz, 1 H, H−COSi, major); 2.40−2.30 (m, 1 H, minor), 2.30−2.10 (m, 1 H, major), 2.05−1.80 (m, 2 H), 1.50−0.80 (m, 6 H), 1.31 (d, J = 6.4 Hz, 3 H, CH_3, major), 1.10 (s, 3 H, CH_3, minor), 0.93 (s, 9 H, *t*Bu, major), 0.92 (s, 3 H, CH_3, major), 0.87 (s, 3 H, CH_3, minor), 0.82 (d, J = 6.3 Hz, 3 H, CH_3, minor), 0.79 (s, 9 H, *t*Bu, major), 0.57 (d, J = 6.6 Hz, 3 H, CH_3, major), 0.48 (s, 3 H, CH_3, major), 0.17 (d, J = 6.6 Hz, 3 H, CH_3, minor), 0.04 (s, 3 H, CH_3, minor), 0.03 (s, 3 H, CH_3, minor), −0.21 (s, 3 H, $SiCH_3$, major), −0.26 (s, 3 H, $SiCH_3$, major). ^{13}C NMR (100 MHz, $CDCl_3$): major isomer, δ 143.4, 142.8, 138.9, 130.7, 128.0, 127.5, 127.2, 126.4, 114.3, 87.4, 72.3, 69.9, 64.2, 36.6, 33.6, 32.1, 28.9, 25.8, 24.8, 23.5, 22.0, 21.3, 20.1, 18.0, −5.5, −5.7; minor isomer, δ 143.2, 142.4, 138.8, 130.8, 128.1, 127.9, 127.2, 126.9, 126.2, 114.3, 87.5, 71.8, 69.8, 64.7, 35.9, 33.6, 31.2, 29.0, 26.0, 25.5, 23.8, 22.1, 20.9, 20.0, 18.3, −5.3, −5.4. FAB-MS: 524.3 (7, $[M + 1]^+$). Anal. Calcd for $C_{33}H_{53}NO_2Si$ (523.87): C, 75.66; H, 10.20; N, 2.67. Found: C, 75.52; H, 10.34; N, 2.69.

2-Methyl-2-[(2-methyl-1-phenylpropyl)(1-phenyl-hex-5-enyloxy)amino]propan-1-ol (6). TBDMS-**6** (200 mg, 0.39 mmol) was dissolved at rt in THF (15 mL) and treated with TBAF·$(H_2O)_3$ (372 mg, 1.18 mmol). The reaction mixture was stirred at RT for 14 h. Saturated aqueous NH_4Cl was added, and the biphasic mixture was extracted three times with Et_2O. The combined organic phases were washed with brine and dried ($MgSO_4$). Evaporation of the solvents and purification by FC (Et_2O/pentane = 1:10) afforded **6**: 132 mg (85%). IR ($CHCl_3$): 2956 s, 2867 m, 1453 m, 1048 s, 915 m cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): both isomers, δ 7.55−7.21 (m, 5 H), 5.78−5.67 (m, 1 H), 5.00−4.89 (m, 2 H), 4.72 (dd, J_1 = 3.9 Hz, J_2 = 10.5 Hz, 1 H, HCPh), 4.62 (dd, J_1 = 4.4 Hz, J_2 = 10.3 Hz, 1 H, HCPh), 3.63 (d, J = 10.8 Hz, 1 H, HCO), 3.36 (d, J = 10.5 Hz, 1 H, HCO), 3.16 (d, J = 10.6 Hz, 1 H, HCO), 3.13−3.08 (m, 1 H, HC(*i*Pr)), 2.89−2.84 (m, 2 H, HC(*i*Pr), HCO), 2.60−1.70 (m, 5 H), 1.34 (d, J = 6.3 Hz, 3 H, CH_3), 1.27 (s, 3 H, CH_3), 1.40−1.00 (m, 2 H), 1.10 (s, 3 H, CH_3), 0.72 (d, J = 6.2 Hz, 3 H, CH_3), 0.68 (s, 3 H, CH_3), 0.58 (d, J = 6.6 Hz, 3 H, CH_3), 0.38 (s, 3 H, CH_3), 0.19 (d, J = 6.6 Hz, 3 H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): both isomers, δ 142.3, 142.1, 141.6, 141.2, 138.4, 130.6, 128.2, 128.2, 128.1, 128.0, 127.7, 127.5, 127.2, 126.9, 126.7, 114.8, 114.7, 87.6, 87.5, 72.8, 72.0, 70.1, 69.6, 63.9, 63.3, 36.0, 35.5, 33.6, 33.5, 31.9, 31.1, 25.7, 25.1, 24.8, 22.2, 21.9, 21.3, 20.8, 20.1, 19.4, 18.0. FAB-MS: 396.3 (100, $[M + 1]^+$). Anal. Calcd for $C_{26}H_{37}NO_2$ (395.58): C, 78.94; H, 9.43; N, 3.54. Found: C, 78.78; H, 9.47; N, 3.36.

***N*-(2-Methyl-1-phenylpropyl)-*N*-(1-methyl-2,6,7-trioxabicyclo[2.2.2]oct-4-yl)-*O*-(1,1-dimethylhex-5-enyl)hydroxylamine (7b).** 6-Iodo-6-methyl-1-heptene (238 mg, 1.0 mmol) and PO3TIPNO[11] (584 mg, 2.0 mmol) were dissolved under Ar in benzene (20 mL) and heated to reflux. Bu_3SnH (0.27 mL, 1.0 mmol) was added in 3 portions in 60 min intervals. After complete addition, stirring was continued for 30 min. Removal of the solvent and purification by FC (Et_2O/pentane = 1:10) afforded **7b**: 216 mg (54%). IR ($CHCl_3$): 2954 s, 1402 s, 1299 s, 1132 s, 1062 m, 874 s cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, two isomers due to chirality center at nitrogen): δ (both isomers) 7.50−7.48 (m, 1 H), 7.36−7.22 (m, 4 H), 5.87−5.76 (m, 1 H), 5.06−4.96 (m, 2 H), 4.05−4.02 (m, 3 H, CHO, isomer A), 4.01−3.94 (m, 3 H, CHO, isomer B), 3.87−3.84 (m, 3 H, CHO, isomer B), 3.53−3.50 (m, 3 H, CHO, isomer A), 2.93 (d, J = 10.4 Hz, 1 H, Ph CHN), 2.32−2.00 (m, 3 H), 1.70−1.00 (m, 16 H), 0.86 (d, J = 6.3 Hz, 3 H, CH_3(*i*Pr), isomer A), 0.46 (d, J = 6.7 Hz, 3 H, CH_3(*i*Pr), isomer B). ^{13}C NMR (100 MHz, $CDCl_3$, both isomers): δ 140.0, 138.7, 138.58, 138.57, 131.0, 128.4, 128.0, 127.8, 127.3, 114.83, 114.80, 108.6, 108.2, 81.7, 81.4, 75.3, 73.6, 68.8, 67.8, 58.3, 58.2, 42.7, 42.3, 34.28, 34.25, 31.2, 29.4, 27.52, 27.49, 26.2, 25.4, 24.2, 23.7, 22.93, 22.89, 22.8, 22.3, 21.6, 21.1. HiResMALDI (M + H): calcd for $C_{24}H_{38}NO_4$ 404.2801, found 404.2793.

2-Hydroxymethyl-2-[(2-methyl-1-phenylpropyl)(1-phenylethyl)amino]propan-1,3-diol (8a). According to GP2 with (1-bromoethyl)benzene (0.22 mL, 1.6 mmol), PO3TIPNO[11] (500 mg, 1.71 mmol), Cu (109 mg, 1.70 mmol), $Cu(OTf)_2$ (5.7 mg, 0.016 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (19.3 mg, 0.12 mmol) in benzene (4.2 mL) for 14 h. Purification by FC (Et_2O/pentane = 1:10) afforded **7a** as mixture of diastereoisomers (∼1:1), 325 mg (51%).

Ortho ester **7a** (320 mg, 0.81 mmol) was dissolved in THF (7.5 mL). H_2O (0.15 mL) and *p*-TosOH·H_2O (7.6 mg) were added, and the reaction mixture was stirred for 30 min at rt. After addition of CH_2Cl_2, the mixture was washed with saturated aqueous $NaHCO_3$ and brine (the aqueous phases were back-extracted (three times) with CH_2Cl_2). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvents afforded the corresponding diol ester, which was subsequently dissolved at rt in glyme (5.5 mL). LiOH (1 N, 1.62 mL) was added, and the solution was stirred for 1.5 h at rt. After addition of saturated aqueous $NaHCO_3$, the mixture was extracted with CH_2Cl_2 (three times). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvents afforded the crude product, which was purified by FC (Et_2O/pentane = 3:1) to yield **8a**, 265 mg (88%). Mp: 96.5−98 °C. IR ($CHCl_3$): 3550 br s, 2979 s, 1452 m, 1046 s cm^{-1}.^{1}H NMR (400 MHz): isomer A, δ 7.70−7.20 (m, 10 H), 5.02 or 4.97 (q, J = 6.7 Hz, 1 H, CHO), 3.80−3.50 (m, 4 H), 3.40−3.30 (m, 3 H), 2.48 (s, br, OH), 2.50−2.40 (m, 1 H), 2.24 (t, J = 6.2 Hz, OH), 1.63 (d, J = 6.6 Hz, 3 H), 1.41 (d, J = 6.4 Hz, 3 H), 0.60 (d, J = 6.4 Hz, 3 H); isomer B, δ 7.70−7.20 (m, 10 H), 5.02 or 4.97 (q, J = 6.7 Hz, 1 H, CHO), 3.80−3.50 (m, 4 H), 3.40−3.30 (m, 3 H), 2.48 (s, br., OH), 2.50−2.40 (m, 1 H), 2.24 (t, J = 6.2 Hz, OH), 1.71 (d, J = 6.7 Hz, 3 H), 0.94 (d, J = 6.3 Hz, 3 H), 0.27 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz): isomer A, δ 142.9, 141.2, 129.0, 128.5, 128.2, 127.5, 126.9, 126.6, 84.0, 72.9, 68.5, 64.8, 32.2, 23.1, 22.0, 21.4; isomer B, δ 143.1, 140.7, 128.7, 128.2, 128.0, 127.4, 84.1, 72.6, 69.5, 64.1, 31.8, 22.9, 21.9, 21.0. HiResMALDI (M + H): calcd for $C_{22}H_{32}NO_4$ 374.2331, found 374.2316. Anal. Calcd for $C_{22}H_{31}NO_4$ (373.49): C, 70.75; H, 8.37; N, 3.75. Found: C, 70.71; H, 8.42; N, 3.74.

2-Hydroxymethyl-2-[(2-methyl-1-phenylpropyl)(1-phenylhept-6-enyloxy)amino]propane-1,3-diol (8b). According to GP2 with PO3TIPNO[11] (470 mg, 1.61 mmol), 1-bromo-1-phenyl-6-heptene (380 mg, 1.50 mmol), 4,4′-di-*tert*-butyl-2,2′-bipyridyl (16.5 mg, 0.06 mmol), Cu (102 mg, 1.59 mmol) and $Cu(OTf)_2$ (5.3 mg, 0.015 mmol) in benzene (4 mL) for 13 h. Purification by FC (Et_2O/pentane = 1:15) afforded the corresponding ortho ester, 384 mg (55%, dr = 1:1). The ortho ester (360 mg, 0.77 mmol) was dissolved in THF (7 mL) at 0 °C. H_2O (0.14 mL) and *p*-TosOH·H_2O (7.2 mg) were added, and the reaction mixture was stirred for 1 h at 0 °C. After addition of CH_2Cl_2 the mixture was washed with saturated aqueous $NaHCO_3$ and brine (the aqueous phases were backextracted (three times) with CH_2Cl_2). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvents afforded the corresponding diol ester, which was subsequently dissolved at rt in glyme (5.2 mL). 1 N LiOH (1.54 mL) was added, and the solution was stirred for 1.5 h at rt. After addition of saturated aqueous $NaHCO_3$ the mixture was extracted with CH_2Cl_2 (three times). Drying of the combined org. layers ($MgSO_4$) and evaporation of the solvents afforded the crude product which was purified by FC (Et_2O/pentane = 3:1) to yield **8b**, 303 mg (89%, dr = 1:1). ^{1}H NMR (400 MHz): both isomers, δ 7.70−7.20 (m, 10), 5.79−5.66 (m, 1 H), 4.98−4.88 (m, 2 H), 4.82 (dd, J_1 = 4.1 Hz, J_2 = 11.2 Hz, 1 H, HC(Ph)O, isomer A), 4.70 (dd, J_1 = 4.1 Hz, J_2 = 11.0 Hz, 1 H, HC(Ph)O, B), 3.80−3.60 (m, 4 H), 3.30−3.20 (m, 3 H), 2.60−2.10 (m, 4 H), 2.10−1.70 (m, 3 H), 1.50−0.90 (m, 3 H), 1.41 (d, J = 6.4 Hz, 3 H), 0.84 (d, J = 6.2 Hz, 3 H), 0.61 (d, J = 6.6 Hz, 3 H), 0.24 (d, J = 6.6 Hz, 3 H). ^{13}C NMR (100 MHz): both isomers, δ 141.3, 141.2, 140.9, 140.7, 138.6, 138.5, 130.3, 128.91, 128.89, 128.4, 128.33, 128.29, 128.0, 127.9, 127.6, 127.5, 127.3, 114.6, 114.5, 88.5, 88.3, 73.1, 72.5, 69.6, 68.3, 64.8, 64.0, 35.53, 35.48, 33.5, 32.2, 31.7, 28.7, 28.6, 25.3, 25.1, 22.0, 21.8, 20.9. FAB-MS: 442.2 (100, $[M + H]^+$). Anal. Calcd for $C_{27}H_{39}NO_4$ (441.61): C, 73.44; H, 8.90; N, 3.17. Found: C, 73.20; H, 8.91; N, 3.22.

2-Hydroxymethyl-2-[(2-methyl-1-phenylpropyl)(1,1-dimethylhex-5-enyl)amino]propane-1,3-diol (8c). Ortho ester **7b** (216 mg, 0.53 mmol) was dissolved in THF (7.5 mL). H_2O (0.15 mL) and *p*-TosOH·H_2O (7 mg) were added, and the reaction mixture was stirred for 30 min at rt. After addition of CH_2Cl_2, the mixture was washed with saturated aqueous $NaHCO_3$ and brine (the aqueous phases were back-extracted (three times) with CH_2Cl_2). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvents afforded the corresponding diol ester, which was subsequently dissolved at rt in glyme (5.5 mL). LiOH (1 N, 1.62 mL) was added, and the solution was stirred for 1.5 h at rt. After addition of saturated aqueous $NaHCO_3$ the mixture was extracted with CH_2Cl_2 (three times). Drying of the combined organic layers ($MgSO_4$) and evaporation of the solvents afforded the crude product which was purified by FC (Et_2O/pentane = 5:1) to yield **8c**, 153 mg (74%). ^{1}H NMR (400 MHz, $CDCl_3$, two isomers due to chirality center at nitrogen, dr ≈ 3:1): δ major isomer, 7.54−7.23 (m, 5 H), 5.87−5.76 (m, 1 H), 5.06−4.96 (m, 2 H), 3.75−3.50 (m, 6 H, CHO), 3.45 (d, J = 10.4 Hz, 1 H, Ph CHN), 2.65−2.50 (m, 4 H), 2.20−1.40 (m, 6 H), 1.45 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 1.20 (d, J = 6.3 Hz, 3 H, CH_3(*i*Pr)), 0.47 (d, J = 6.7 Hz, 3 H, CH_3(*i*Pr)); δ minor isomer, 7.54−7.23 (m, 5 H), 5.87−5.76 (m, 1 H), 5.06−4.96 (m, 2 H), 4.18 (d, J = 11.6 Hz, 1 H, PhCHN), 3.75−3.50 (m, 6 H, CHO), 2.65−2.50 (m, 4 H), 2.20−1.40 (m, 6 H), 1.47 (s, 3 H, CH_3), 1.34 (d, J = 6.5 Hz, 3 H, CH_3(*i*Pr)), 0.80 (d, J = 6.4 Hz, 3 H, CH_3(*i*Pr)). ^{13}C NMR (100 MHz, $CDCl_3$): δ major isomer, 140.9, 138.4, 130.9, 127.8, 127.2, 115.0, 83.1, 72.6, 69.7, 64.3, 42.6, 34.3, 31.8, 27.3, 26.2, 24.5, 22.4, 21.3; δ minor isomer, 139.7, 138.4, 128.2, 127.5, 115.0, 82.7, 75.8, 70.9, 63.1, 42.5, 34.2, 31.6, 27.3, 25.7, 24.0, 23.2, 21.2. HiResMALDI (M + H): calcd for $C_{22}H_{38}NO_4$ 380.2801, found 380.2788.

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