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Normal, Leveled, and Enhanced Steric Effects in Alkoxyamines Carrying a β-Phosphorylated Nitroxyl Fragment

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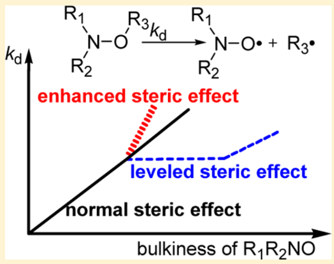
Supporting Information

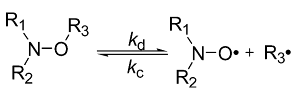
ABSTRACT: The design of new $R_1R_2NOR_3$ alkoxyamines for various applications relies on the accurate prediction of two kinetic parameters, the C−ON bond homolysis rate constant (k_d) and its re-formation rate constant (k_c). Relationships to describe the steric and polar effects of the R_1R_2NO fragment ruling k_d have been developed. For all cyclic nitroxyl fragments, the steric effect is described as the sum of the bulkiness of the R_1 and R_2 groups (i.e., normal steric effect), while for the noncyclic nitroxyl fragment (except for one case), a leveled steric effect is assumed. In this work, we show that the normal steric effect also applies to noncyclic nitroxyl fragments and that for one case an enhanced steric effect is also observed, i.e., experimental k_d >5-fold larger than the predicted value.



■ INTRODUCTION

For several decades,[1] alkoxyamines and their fascinating properties (Scheme 1), i.e., C−ON bond homolysis (rate constant k_d) to generate an alkyl radical and a nitroxide and re-formation via a cross-coupling reaction (rate constant k_c), have found applications in various fields such as material sciences (as self-healing polymers,[2,3] materials for photonics,[4] and coding systems[5,6]), polymer sciences,[1,7,8] chemistry (as tin free reagents),[9,10] and biology[11,12] [as theranostic agents (Figure 1)].

Scheme 1



For the application of alkoxyamines as theranostic agents, the concept of "smart" alkoxyamines was devised (Figure 2);[12] that is, it relies on the switch from a stable to a highly labile alkoxyamine upon an external chemical or biochemical triggering event. However, to circumvent the issues related to the diffusion of alkoxyamines in tissues, a very fast homolysis is required, i.e., a half-lifetime of a few seconds.[12] In alkoxyamines, the increasing bulkiness of both alkyl and nitroxyl fragments and increasing the polarity in the alkyl fragment lead to an increased k_d, and conversely, in released radicals, i.e., alkyl radicals and nitroxides, increasing their level of stabilization also affords an increase in k_d.[13] At first glance, the polar effect is the easiest effect to modify almost reversibly. On the basis of this assumption, the activation of C−ON bond homolysis by increasing the polarity of the alkyl fragments was highlighted using protonation,[14] alkylation,[14] acylation,[14] complexation with an inorganic Lewis acid,[14] and complexation with metal salts[15,16] to afford an up to 30−40-fold increase in k_d. In the same way, deprotonation[17,18] and decomplexation[16] of the nitroxyl fragment afforded a moderated 10-fold increase in k_d. However, we recently showed that a strong effect of polarity of the alkyl fragment requires strong electron-widthdrawing groups (EWGs) carried by the nitroxyl fragment.[19] By contrast, eq 1[20] shows that k_d decreases with an increase in polarity (and a decrease in the level of stabilization of the nitroxide). Nevertheless, **2**-based alkoxyamines seem to be promising candidates, because of the presence of strong EWGs and a bulky diethylphosphoryl group on the alkyl and nitroxyl fragments.[21] However, the leveling of the steric effect[20,22−24] cancels all benefits because of the bulkiness and polarity of the diethylphosphoryl group. It has been noted[20,24−26] that this leveled steric effect occurs mainly for noncyclic nitroxides carrying a H atom at position β.

$$\log[k_d\ (s^{-1})] = -5.88(\pm 0.28) - 3.07(\pm 0.28)\sigma_I - 0.88(\pm 0.04)E_s \qquad (1)$$

As far as we know, only the synthesis of **3** has been reported in the literature,[27] which led us to design alkoxyamines **4**−**9** (Figure 3) and to investigate the effect of a change in both bulkiness (**3**−**6**) and polarity (**5** and **7**, **6** and **8**, and **9**). Besides

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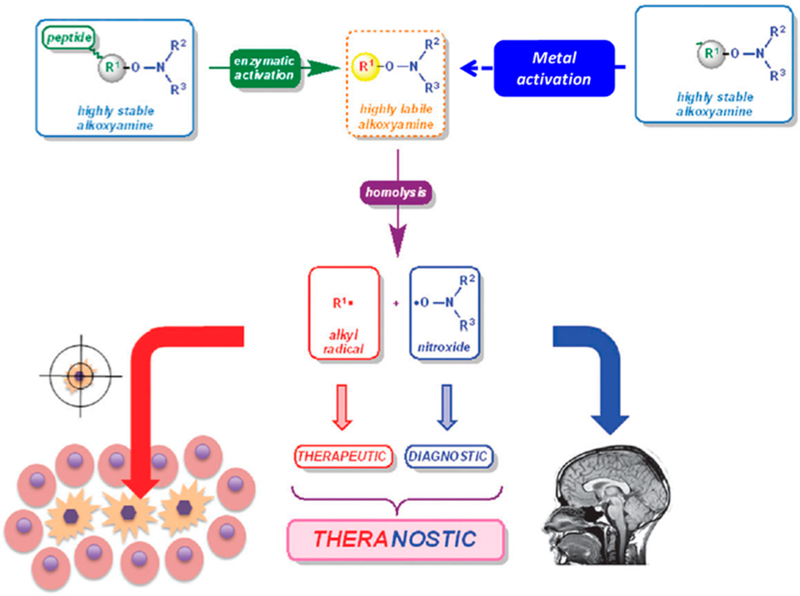

Figure 1. Concept for the use of alkoxyamines as theranostic agents based on enzymatic or metal ion activation. Reproduced with permission from ref 12. Copyright 2014 Royal Society of Chemistry.

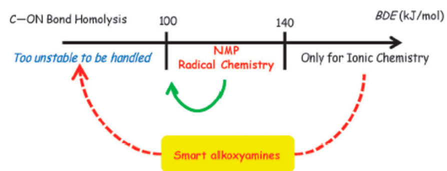

Figure 2. Requirements for smart alkoxyamines. Reproduced with permission from ref 12. Copyright 2014 Royal Society of Chemistry.

the development of alkoxyamines for theranostic applications, this work has a more fundamental aspect. Indeed, the design of alkoxyamines relies on the ability to predict k_d and k_c[28] depending on the application that is being targeted. For a decade, both empirical[20,29] and theoretical[30] reactivity–structure relationships have been developed. Indeed, eq 1[31] (with the σ_I electrical Hammett constant used to describe the effect of EWGs on both the stabilization of the released nitroxide and the change in polarity in the alkoxyamine and E_s to account for the bulkiness of the nitroxyl fragment)[32] relies on the assumption of a linear change in the steric effect, from alkoxyamine **1** carrying a noncyclic nitroxyl fragment to alkoxyamine **12** carrying a cyclic nitroxyl fragment. It is assumed that the bulkiness of each of the groups attached to the nitroxyl moiety is given by eq 2[33] and that their sum (eq 3)[34] accounts for the bulkiness of the alkyl fragment. However, among all alkoxyamines carrying noncyclic nitroxyl fragments, **1** is the only one that fulfils these requirements! The results discussed hereafter highlight the fact that eqs 1–3 apply to many types of alkoxyamines except those similar to alkoxyamines **2** and **14**.

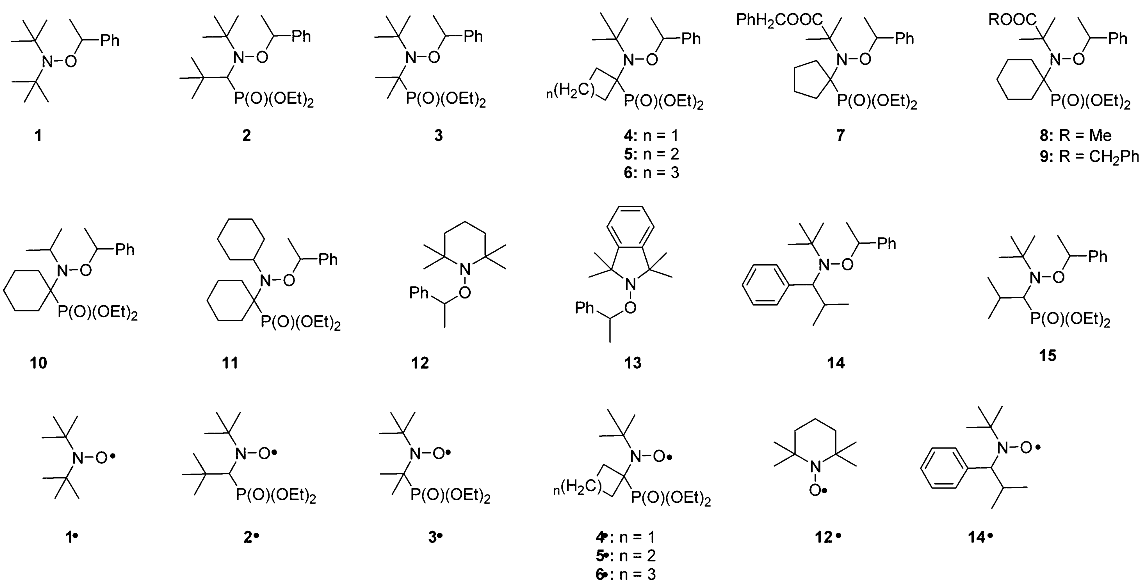

Figure 3. Alkoxyamines and nitroxides discussed in this work.

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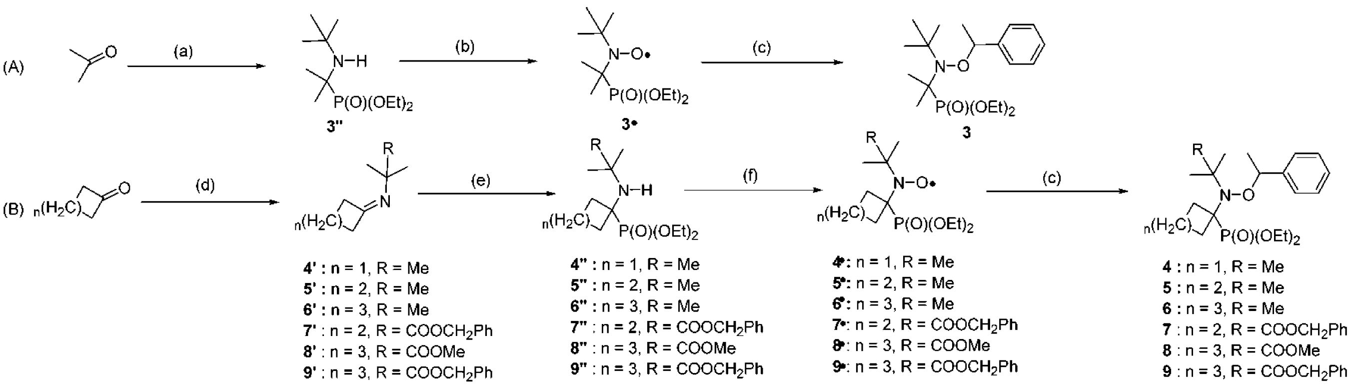
Scheme 2. (A) Preparation of 3[a], and of 4−9[b]



[a](A) Preparation of **3**: (a) *t*-$BuNH_2$, $HP(O)(OEt)_2$ neat, 0 °C, 77%; (b) *m*CPBA, CH_2Cl_2, −78 °C, 5 h, 7%; (c) PhCHBrMe, CuBr, PMEDTA, Cu(0), benzene, 55−80%. [b](B) (d) $H_2NCMe_2CH_2COOR$, $TiCl_4$, DCM, 0 °C; (e) $HP(O)(OEt)_2$, 40 °C, 52−90%; (f) *m*CPBA, $CHCl_3$, 56−80%.

Table 1. Experimental C−ON Bond Homolysis Rate Constants (k_d') for Alkoxyamines 3−9 in Toluene,[a] Activation Energies (E_a), Re-Estimated Rate Constants (k_d), Polar/Stabilization Hammett-Type Constants ($\sigma_{I,n}$), and Taft Steric Constants (E_s) for 1−12

	T (°C)[b]	k_d' ($\times 10^{-4}$ s^{-1})	E_a (kJ/mol)[c]	k_d ($\times 10^{-3}$ s^{-1})[d]	$\sigma_{I,n}$[e,f]	E_s[e,g,h,i]	refs
1			122.4	12.9	−0.06	−4.21	20, 21
2			125.5	5.0	0.28	−5.0[j]	20, 21
3	70	1.6	119.3	33.4	0.27	−5.0	this work
4	79	0.5	125.6	4.9	0.27	−5.21	this work
5	67	1.3	118.9	37.7	0.27	−5.81	this work
6	55	1.4	114.5	144.9	0.27	−6.46	this work
7	80	6.8	125.4	5.2	0.60	−5.81[k]	this work
8	80	3.4	120.7	21.7	0.60	−6.46[k]	this work
9	80	2.9	121.1	19.3	0.60	−6.46[k]	this work
10			126.6	3.6	0.28	−5.36	20, 21
11			125.8	4.6	0.28	−5.36	20, 21
12			132.9	0.5	−0.06	−2.70	20, 21

[a]No solvent effect is considered between toluene and *tert*-butylbenzene, the solvent for which literature data were reported. [b]Within ±1 °C. [c]Estimated using values reported in the third column and using a frequency factor A of 2.4×10^{14} s^{-1}. See ref 21. [d]Estimated at 120 °C using values reported in the fourth column and using frequency factor A of 2.4×10^{14} s^{-1}. See ref 21. [e]$\sigma_{I,n}$ and E_s values are estimated as described in ref 20. [f]Individual values of σ_I are given in ref 38: $\sigma_{I,H} = 0$, $\sigma_{I,Me} = \sigma_{I,t\text{-}Bu} = -0.01$, $\sigma_{I,COOR} = \sigma_{I,COOMe} = 0.32$, and $\sigma_{I,P(O)(OEt)_2} = 0.32$. [g]Individual steric constants r are given in refs 20 and 40: r(H) = 0.32, r(Me) = 0, $r[(CH_2)_4] = -0.04$, $r[(CH_2)_5] = -0.15$, $r[(CH_2)_6] = -0.27$, $r[P(O)(OEt)_2] = 1.22$, and r(*t*-Bu) = −2.46. [h]As the value of 1.04 for $\upsilon[P(O)(OEt)_2]$ is close to the value of 1.02 for $\upsilon(^sBu)$, assuming a value of −1.22 for $r[P(O)(OEt)_2]$ is reasonable, because it is close to the $r(^sBu)$ of −1.25. See refs 39 and 40. [i]E_s values are estimated assuming that eqs 2 and 3 hold unless otherwise mentioned. [j]Assuming the leveled steric effect. See ref 20. [k]It is assumed that r(COOBn) ≈ r(COOMe) ≈ r(Me) as υ(COOMe) = 0.50 and υ(Me) = 0.52. See ref 41.

$$E_s^{A\text{ or }B} = -2.104 + 3.429r(R_1) + 1.978r(R_2) + 0.649r(R_3) \quad (2)$$

$$E_{s,n} = aE_s^{A} + bE_s^{B} + \varepsilon \quad (3)$$

■ RESULTS

Preparation of 3−9. Nitroxides **3•**[35] (Scheme 2A) and **4•**[35] through **6•**[36] (Scheme 2B) were prepared as previously reported. Nitroxides **7•**−**9•** were prepared from the corresponding cyclic ketones that were transformed into corresponding imines **7′**−**9′**, respectively, and then into phosphorylated amines **7″**−**9″**, respectively, as colorless oils (Scheme 2B). The latter were oxidized with *m*-chloroperbenzoic acid (*m*CPBA) into nitroxides **7•**−**9•** in rather moderate yields as orange oils (Scheme 2B, 33% for **7•**, 30% for **8•**, and 37% for **9•** as overall yields). Alkoxyamines **3**−**9** (Scheme 2) were prepared using Matyjaszewski's procedure as colorless oils in moderated to good yields (55% for **3** to 80% for **7**).[37] No attempts were made to grow crystals.

Kinetic Measurements. Values of k_d' were measured by NMR using **12•** as an alkyl radical scavenger as previously reported.[13] Values of k_d and E_a for **1**−**12** are listed in Table 1 along with k_d' values for **3**−**9**. A clear decrease in E_a is observed with the increase in ring size from **4** to **6** (Table 1). This decrease is again observed from **7** to **9**. Moreover, the size of the ester group has no significant effect, i.e., E_a of **9** similar to E_a of **8**.

Multiparameter Relationships. Parameters $\sigma_{I,n}$[20,38] and $E_{s,n}$[20] are estimated as previously reported (Table 1). Individual steric constants r(C4), r(C5), and r(C6) are used to account for the steric effect of the four-, five-, and six-membered rings, respectively, attached to the nitroxyl moiety.[40] The nonsignificant difference in E_a between **8** (R = Me) and **9** (R = CH_2Ph) and the very close steric constants for the ester and methyl groups, i.e., υ(COOR) = 0.50 and υ(Me) = 0.52,[41]

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support the assumption that $E_s(COOR) \approx E_s(Me)$. In previous work, it was noticed that the leveled steric effect occurs for all alkoxyamines carrying a diethylphosphoryl group and has to be taken into account in estimating E_s values. Moreover, it was mentioned that the leveled effect is likely to occur for alkoxyamines exhibiting E_s values smaller than −6, which is the case for **6**, **8**, and **9**. Thus, when the assumption of the leveled steric effect holds, E_s for **4**−**9** is given as −5.0, as they are very similar to the values of **10** and **11**. When $\sigma_{I,n}$ and $E_{s,n}$ for **4**−**9** are implemented in eq 1, a scattered plot is observed (blue empty circles in Figure 4), except for **4**, which is lying close to the correlation line. When the leveled steric effect is not taken into account and eqs 2 and 3 are applied straightforwardly, a very good correlation (eq 4)[42] is observed, considering **3** as an outlier (Figure 4).[43] As good statistical outputs and very similar coefficients are observed for eq 4 as well as for eq 1, the weight of each effect is not re-estimated. All this is undeserving of more comment. Importantly, the meaningfulness of the correlation is also highlighted by the range of values covered by $\sigma_{I,n}$ and $E_{s,n}$, i.e., $-0.06 < \sigma_{I,n} < 0.60$, $-6.5 < E_{s,n} < -2.1$, and $1.5 < f(\sigma_{I,n},E_{s,n}) < 5.0$, and the 4 order of magnitude changes in k_d.

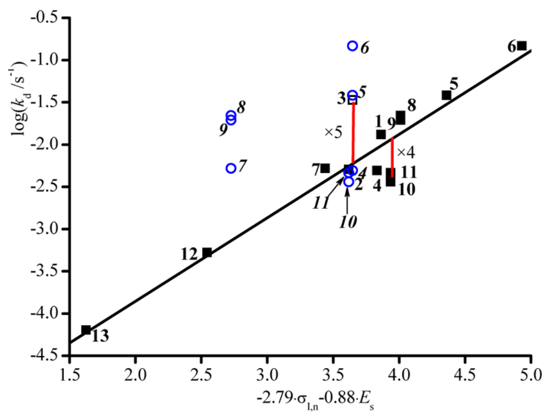

Figure 4. Plot of $\log[k_d\ (s^{-1})]$ vs $f(\sigma_{I,n},E_s)$ for **1**−**12**. Bold squares are for values listed in Table 1. Italicized numbers and empty blue circles are for values when the leveled steric effect holds. The empty square is for outliers. Vertical red lines are used to visualize the deviation from the correlation.

$$\log[k_d\ (s^{-1})] = -5.90(\pm 0.15) - 2.79(\pm 0.25)\sigma_{I,n} - 0.88(\pm 0.04)E_{s,n} \quad (4)$$

■ DISCUSSION

Applying eqs 2 and 3 to describe the steric effect in **4**−**9** and then eq 1 yields a very good correlation (eq 4 and Figure 4), with almost all data lying on the correlation line, except the value of **4**, which is overestimated by a factor of 2 in the error range, i.e., a difference of <2 kJ between predicted and experimental data. This straightforward approach is also applied to **10** and **11**, affording data deviating by a factor of <4. These results highlight nicely the versatility and the robustness of eqs 1−3 to describe the effects involved in changes in k_d, making only a few assumptions.[20,24] They also highlight the generality of eqs 2 and 3 which apply to cyclic and noncyclic nitroxyl fragments.

Amazingly, eqs 1−3 cannot describe the steric effect for the very simple case of **3**, which differs from **1** by one methyl group replaced with a diethylphosphoryl group (Figure 4). Whatever the assumption, with or without the leveled effect, the k_d of **3** is >5-fold underestimated by eq 1 (Figure 4), meaning that $r[P(O)(OEt)_2]$ is larger than the recommended values, i.e., $r[P(O)(Et)_2] = -2.47$, assuming **3** lies on the correlation line. The $r[P(O)(OEt)_2]$ value of −1.22 was determined assuming **2** lies on the correlation line and found to be in good agreement with those from the literature (footnote h in Table 1). Moreover, the steric effect of 16 *β*-phosphorylated nitroxyl fragments is captured by eq 4 using this value that has no reason to vary suddenly, up to $r = -2.47$. From our experience, the conformation observed around the nitroxyl moiety in a nitroxide does not differ too much from that observed in the corresponding alkoxyamine.[44] Fortunately, the effects of the solvent on phosphorus hyperfine coupling constant a_P have recently been reported for $2^\bullet$[45] through $6^\bullet$[35] and show striking differences between nitroxides; that is, a_P varies from alkanes to polar solvents between 46 and 47 G, between 42 and 20 G, between 55 and 60 G, between 52 and 53 G, and between 55 and 60 G for $2^\bullet$[45] through $6^\bullet$, respectively.[35] Obviously, $3^\bullet$ experiences a solvent effect strikingly different from that for $2^\bullet$ and $4^\bullet$−$6^\bullet$. a_P is due to the hyperconjugation between the SOMO and the bonding/antibonding $\sigma_{C-P}/\sigma^*_{C-P}$ orbital of the C−P bond (Figure 5), meaning that the better the overlap, the more favored the *syn* periplanar conformation, the stronger the interaction, and the higher the a_P.[35,45−48] Consequently, similar and high values of a_P for $2^\bullet$ and $4^\bullet$−$6^\bullet$ imply the C−P bond is almost *syn* periplanar to the SOMO, as depicted in Figure 6. Moreover, the large change in a_P observed for $3^\bullet$, in sharp contrast to that observed for $2^\bullet$ and $4^\bullet$−$6^\bullet$, points at a strongly less restricted N−CP bond rotation compared to that in $2^\bullet$ and $4^\bullet$−$6^\bullet$, thus affording a very different conformation for $3^\bullet$ and for $2^\bullet$ and $4^\bullet$−$6^\bullet$ (Figure 6). As very close conformations are expected for the corresponding alkoxyamines, a similar bulkiness is expected for the diethylphosphoryl group in **2** and **4**−**6**, as shown by the good observed correlation. The enhanced steric effect observed for **3** is due to a different and more strained conformation, in which the diethylphosphoryl group is directed toward the alkyl fragment, providing a greater bulkiness and thus a greater steric effect, than in **2** and **4**−**6**, because of a subtle interplay between the steric repulsion of the different groups.

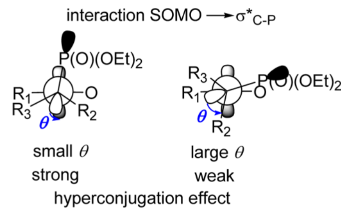

Figure 5. Hyperconjugation effect due to the SOMO → σ^*_{C-P} interaction in nitroxyl radicals. Blue denotes dihedral angle θ, the angle between the C−P bond and the SOMO orbital centered on the nitrogen atom.

■ CONCLUSION

This work highlights the robustness and versatility of eq 1 as the bulkiness of each fragment attached to the nitroxyl moiety is described by the addition of parameters used to describe the

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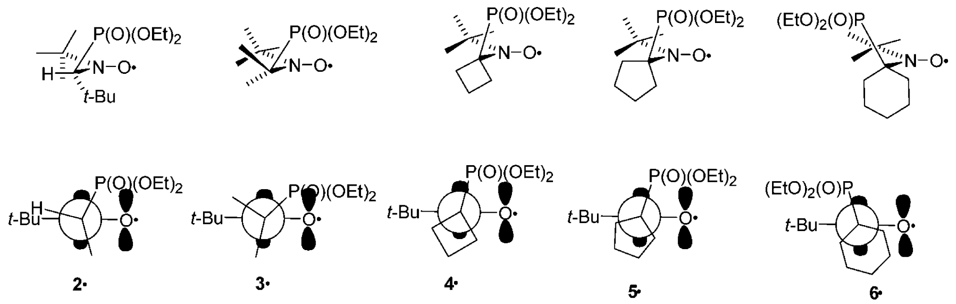

Figure 6. Conformations in nitroxides 2•−6•. Bold orbitals for the SOMO.

steric effect (eqs 2 and 3, the so-called normal steric effect) as well as the boundaries of this approach. That is, the normal steric effect is replaced either by the enhanced steric effect (k_d higher than that predicted as highlighted by alkoxyamine **3** in Figure 4) or by the leveled steric effect (k_d lower than that predicted as highlighted in previous work).[20,24,49] The rules proposed to describe the steric effect in a previous work need to be revised and completed. Indeed, we proposed (i) if the nitroxyl moiety shows some symmetry or pseudosymmetry, ε is equal to zero and (ii) if the nitroxyl moiety does not show any symmetry or pseudosymmetry, ε is equal to $-bE_s^B$. For the time being, it seems that rule (i) applies when E_s (estimated with eqs 3 and 4) does not exceed −6.

Keeping in mind a predictive use of eqs 1−3, we propose amended rules. (i) Equations 1−3 with $\varepsilon = 0$, i.e., normal steric effect,[20,24,50] hold for alkoxyamines exhibiting two tertiary carbon atoms attached to the nitroxyl moiety.[51] (ii) Equations 1−3 with $\varepsilon = -bE_s^B$, i.e., leveled steric effect,[20,24,50] hold for alkoxyamines exhibiting a tertiary carbon atom and a secondary carbon atom attached to the nitroxyl moiety (this rule is supported by the normal steric effect observed for **6**, which exhibits a *t*Bu group attached to the nitroxyl moiety, whereas the leveled steric effect[20] is observed for **10**, which exhibits an *i*Pr group attached to the nitroxyl moiety). (iii) The enhanced steric effect might be expected for alkoxyamine exhibiting two tertiary carbon atoms attached to the nitroxyl moiety and C−N bonds exhibiting low rotational barriers.

This improved description of the steric effect in the alkoxyamine C−ON bond homolysis is important and needed for the design of new alkoxyamines suitable for more efficient NMP under various conditions,[8] to develop smart materials[3−6] or to favor new applications in biology.[11]

■ EXPERIMENTAL SECTION

All solvents and reactants for the preparation of alkoxyamines were used as received. Routine reaction monitoring was performed using silica gel 60 F_{254} TLC plates; spots were visualized upon exposure to UV light and a phosphomolybdic acid solution in EtOH as stain revealed by heating. Purifications were performed on chromatography columns with silica gel grade 60 (230−400 mesh) for alkoxyamines **3**−**6**. Purifications of **7″**−**9″**, **7•**−**9•**, and **7**−**9** were performed with a Reveleris X2 flash system (Büchi): a solvent delivery system equipped with high-pressure HPLC pumps, four independent channels with up to four solvents in a single run, autoswitch lines when solvent is depleted, normal phase and reversed phase compatible; pump flow rate of 1−200 mL/min; maximal pressure of 200 psi; linear gradients (the same gradient was used for all purifications, and an example of the profile is provided in Figure S1); sample injection in liquid sample mode; UV wavelength range of 200−500 nm; holds two racks, with automatic rack recognition for the fraction collection; cartouches flash Reveleris et GraceResolv of silica 40 μm. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ on a 300 or 400 MHz spectrometer. Chemical shifts (δ) in parts per million were reported using residual nondeuterated solvents as an internal reference for ^{1}H and ^{13}C NMR spectra and 85% H_3PO_4 for ^{31}P NMR spectra. High-resolution mass spectra were recorded on a SYNAPT G2 HDMS (Waters) spectrometer equipped with a pneumatically assisted atmospheric-pressure ionization source (API). Positive mode electrospray ionization was used on samples: electrospray voltage (ISV), 2800 V; opening voltage (OR), 20 V; nebulizer gas pressure (nitrogen), 800 L/h. Low-resolution mass spectra were recorded on the ion trap AB SCIEX 3200 QTRAP instrument equipped with an electrospray source. Parent ion $[M + H]^+$ is quoted.

General Procedure for the Preparation of Aminophosphorylated Compounds 4″−9″. To a stirred solution of cyclic ketone (1 equiv) and aminoester (5 equiv) in Et_2O was added a solution of $TiCl_4$ (0.7 equiv) in dichloromethane (DCM) at 0 °C. The resulting suspension was stirred at room temperature overnight. The reaction was then quenched with 0.5 M NaOH, and the product was then extracted with Et_2O. The layers were separated; the organic phase was washed with brine and dried over $MgSO_4$, and the solvent was evaporated. Diethylphosphite (2 equiv) was added to crude **4′**−**9′**, and the reaction mixture was left overnight at 40 °C. Unreacted diethylphosphite was evaporated, and the residual oil was purified by flash chromatography to yield the corresponding aminophosphonates **3″**−**9″**. NMR data of **3″**−**6″** are in good agreement with those from the literature.[35,36]

Benzyl 2-(Diethylphosphoryl)-2-[(cyclopentyl)amino]-2-methylpropionate (7″). Cyclopentanone (348 mg, 4.14 mmol, 1 equiv), benzyl aminoester (4.0 g, 20.7 mmol, 5 equiv), $TiCl_4$ (549 mg, 2.90 mmol, 0.7 equiv), Et_2O (20 mL), and diethylphosphite (1.14 g, 8.28 mmol, 2 equiv) were used. After flash chromatography [gradient, petroleum ether (PE)/AcOEt, from 0 to 100% AcOEt], aminophosphonate **7′** was isolated (856 mg, 52%, colorless oil): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (m, 5H), 5.06 (s, 2H), 4.04 (p, J = 7.2 Hz, 4H), 2.02 (m, 2H), 1.84 (s, 1H), 1.56 (m, 6H), 1.33 (s, 6H), 1.22 (t, J = 7.1 Hz, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.44; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.3 (d, J_{C-P} = 2.4 Hz), 136.1, 128.6, 128.2, 66.6, 63.7 (d, J_{C-P} = 161.1 Hz), 62.3 (d, J_{C-P} = 7.8 Hz), 58.3 (d, J_{C-P} = 5.4 Hz), 36.4 (d, J_{C-P} = 5.1 Hz), 28.0, 25.2 (d, J_{C-P} = 7.4 Hz), 16.6 (d, J_{C-P} = 5.5 Hz); HRMS m/z (ESI) calcd for $C_{20}H_{33}NO_5P$ $[M + H]^+$ 398.2091, found 398.2090.

Methyl 2-(Diethylphosphoryl)-2-[(cyclohexyl)amino]-2-methylpropionate (8″). Cyclohexanone (838 mg, 8.54 mmol, 1 equiv), methyl aminoester (5.0 g, 42.68 mmol, 5 equiv), $TiCl_4$ (1.13 g, 5.97 mmol, 0.7 equiv), Et_2O (20 mL), and diethylphosphite (2.35 g, 17.07 mmol, 2 equiv) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt), aminophosphonate **8″** was isolated (1.60 g, 56%, colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.03 (p, J = 7.2 Hz, 4H), 3.62 (s, 3H), 1.71 (m, 7H), 1.46 (m, 4H), 1.35 (s, 6H), 1.25 (t, J = 7.1 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.93; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.3 (d, J_{C-P} = 3.7 Hz), 61.9 (d, J_{C-P} = 7.9 Hz), 58.7 (d, J_{C-P} = 3.8 Hz), 57.1 (d, J_{C-P} = 146.8 Hz), 51.8, 32.6 (d, J_{C-P} = 3.2 Hz), 28.2, 26.0, 20.6 (d, J_{C-P} = 7.9 Hz), 16.7 (d, J_{C-P} = 5.6 Hz); HRMS m/z (ESI) calcd for $C_{15}H_{31}NO_5P$ $[M + H]^+$ 336.1934, found 336.1934.

Benzyl 2-(Diethylphosphoryl)-2-[(cyclohexyl)amino]-2-methylpropionate (9″). Cyclohexanone (416 mg, 4.24 mmol, 1 equiv),

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benzyl aminoester (4.1 g, 21.22 mmol, 5 equiv), $TiCl_4$ (563 mg, 2.97 mmol, 0.7 equiv), Et_2O (20 mL), and diethylphosphite (1.17 g, 8.48 mmol, 2 equiv) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt), aminophosphonate **9″** was isolated (925 mg, 53%, colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.14 (s, 2H), 4.09 (p, J = 7.2 Hz, 4H), 1.60 (m, 10H), 1.44 (s, 6H), 1.29 (t, J = 7.0 Hz, 6H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.51; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5 (d, J_{C-P} = 3.3 Hz), 133.4, 125.8, 125.5, 125.1, 125.1, 63.4, 58.9 (d, J_{C-P} = 8.0 Hz), 55.7 (d, J_{C-P} = 4.0 Hz), 54.1 (d, J_{C-P} = 148.0 Hz), 29.6 (d, J_{C-P} = 3.2 Hz), 25.2, 22.8, 17.7 (d, J_{C-P} = 7.5 Hz), 13.6 (d, J_{C-P} = 5.5 Hz); HRMS m/z (ESI) calcd for $C_{21}H_{35}NO_5P$ [M + H]$^+$ 412.2247, found 412.2245.

General Procedure for Oxidation of 4″–9″ to 4•–9•. To a stirred solution of aminophosphonates **4″–9″** (1 equiv) in chloroform was added a solution of mCPBA (1.5 equiv) in chloroform. The reaction mixture was strirred at room temperature for 3 h and then the reaction quenched with 10% Na_2SO_3 in water. Nitroxides **4•–9•** were extracted with DCM. The layers were separated; the organic phase was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. The solvents were evaporated, and the product was purified by flash chromatography to yield the corresponding nitroxides **4•–9•**. EPR and HRMS data of **3•–6•** are in good agreement with those from the literature.[35,36]

*N,N-(1-Methyl-1-benzylcarboxyethyl)(1-diethylphosphorylcyclopentyl)amino-N-oxyl Radical (**7•**).* Aminophosphonate **7″** (500 mg, 1.26 mmol, 1 equiv), 77% mCPBA (422 mg, 1.89 mmol, 1.5 equiv), and chloroform (10 mL) were used. The solvents were evaporated, and the product was purified by flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt) to afford nitroxide **7•** (330 mg, 64%, orange oil): HRMS m/z (ESI) calcd for $C_{20}H_{32}NO_6P$ [M + H]$^+$ 413.1962, found 413.1961.

*N,N-(1-Methyl-1-methylcarboxyethyl)(1-diethylphosphorylcyclohexyl)amino-N-oxyl Radical (**8•**).* Aminophosphonate **8″** (415 mg, 1.24 mmol, 1 equiv), 77% mCPBA (416 mg, 1.86 mmol, 1.5 equiv), and chloroform (10 mL) were used. The solvents were evaporated, and the product was purified by flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt) to afford the corresponding nitroxides **8•** (228 mg, 53%, orange oil): HRMS m/z (ESI) calcd for $C_{15}H_{30}NO_6P^\bullet$ [M + H]$^+$ 351.1805, found 351.1805.

*N,N-(1-Methyl-1-benzylcarboxyethyl)(1-diethylphosphorylcyclohexyl)amino-N-oxyl Radical (**9•**).* Aminophosphonate **9″** (475 mg, 1.15 mmol, 1 equiv), 77% mCPBA (388 mg, 1.73 mmol, 1.5 equiv), and chloroform (10 mL) were used. The solvents were evaporated, and the product was purified by flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt) to afford the corresponding nitroxides **9•** (333 mg, 68%, orange oil): HRMS m/z (ESI) calcd for $C_{21}H_{34}NO_6P$ [M + H]$^+$ 427.2118, found 427.2118.

General Procedure for the Preparation of Alkoxyamines 3–9. To a suspension of CuBr (0.55 equiv) and Cu powder (1.1 equiv) in degassed benzene (3 mL) under argon was added N,N,N',N',N''-pentamethyldiethylenetriamine (0.55 equiv). After being stirred for 10 min, a solution of nitroxides **3•–9•** (1 equiv) and bromoethylbenzene (1.1 equiv) in degassed benzene (argon bubble in benzene for 1 h) (3 mL) was transferred to the first solution. The mixture was allowed to stir for 12 h. The solution was diluted with EtOAc, the reaction quenched with saturated NH_4Cl, and the mixture washed with water and brine and dried over $MgSO_4$. The solvents were evaporated under reduced pressure. The crude product was purified by automatic flash chromatography to yield the corresponding alkoxyamines **3–9**.

*Diethyl {2-[tert-Butyl(1-phenylethoxy)amino]propan-2-yl}-phosphonate (**3**).* CuBr (50.2 mg, 0.35 mmol, 0.55 equiv), Cu powder (44.48 mg, 0.7 mmol, 1.1 equiv), benzene (2 × 3 mL), N,N,N',N',N''-pentamethyldiethylenetriamine (0.073 mL, 0.35 mmol, 0.55 equiv), **3•** (170 mg, 0.64 mmol, 1 equiv), and bromoethylbenzene (130 mg, 0.7 mmol, 1.1 equiv) were used. After purification by column chromatography [dichloromethane (DCM)/MeOH, from 0 to 10% MeOH by 1% step], **3** was obtained in 55% yield (130 mg, colorless oil): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (m, 5H), 5.24 (q, J = 5.9 Hz, 0.56H), 4.99 (J = 6.2 Hz, 0.41H), 4.06 (m, 4H), 1.43 (d, J = 6.6 Hz, 3H), 1.40–1.13 (m, 18H), 1.01 (s, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 30.56, 29.90; ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 144.3, 128.1, 128.0, 127.4, 127.0, 126.8, 82.6, 80.1, 66.2, 65.8, 64.7, 64.3, 63.0, 62.9, 62.3, 62.2, 62.1 (d, J_{C-P} = 7.6 Hz), 61.6 (d, J_{C-P} = 7.4 Hz), 30.4, 29.7, 27.6, 26.9, 25.5, 24.8, 22.0, 16.6 (t, J = 5.8 Hz); HRMS m/z (ESI) calcd for $C_{19}H_{35}NO_4P$ [M + H]$^+$ 372.2298, found 372.2298.

*Diethyl {1-[tert-Butyl(1-phenylethoxy)amino]cyclobutyl}-phosphonate (**4**).* CuBr (139.14 mg, 0.97 mmol, 0.55 equiv), Cu powder (123.92 mg, 1.95 mmol, 1.1 equiv), benzene (2 × 3 mL), N,N,N',N',N''-pentamethyldiethylenetriamine (0.2 mL, 0.97 mmol, 0.55 equiv), **4•** (495 mg, 1.77 mmol, 1 equiv), and bromoethylbenzene (360.9 mg, 1.95 mmol, 1.1 equiv) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 60% AcOEt by 5% step), **4** was obtained in 71% yield as a colorless oil (479 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42–7.14 (m, 5H), 4.88 (q, J = 6.4 Hz, 1H), 4.32–4.08 (m, 4H), 2.88–2.60 (m, 2H), 2.42–2.23 (m, 2H), 1.98 (dd, J = 19.3, 9.6 Hz, 1H), 1.64 (dd, J = 21.8, 11.4 Hz, 1H), 1.45 (d, J = 6.5 Hz, 3H), 1.36 (q, J = 7.6 Hz, 6H), 1.19 (s, 9 H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.14; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 128.1, 127.0, 126.6, 67.5, 65.4, 62.0 (m), 61.3 (d, J_{C-P} = 6.2 Hz), 28.7, 22.8, 16.6 (m), 14.9; HRMS m/z (ESI) calcd for $C_{20}H_{35}NO_4P$ [M + H]$^+$ 384.2298, found 384.2297.

*Diethyl {1-[tert-Butyl(1-phenylethoxy)amino]cyclopentyl}-phosphonate (**5**).* CuBr (117.63 mg, 0.82 mmol, 0.55 equiv), Cu powder (104.22 mg, 1.64 mmol, 1.1 equiv), benzene (2 × 3 mL), N,N,N',N',N''-pentamethyldiethylenetriamine (0.17 mL, 0.82 mmol, 0.55 equiv), **5•** (436 mg, 1.49 mmol, 1 equiv), and bromoethylbenzene (309.49 mg, 1.64 mmol, 1.1 equiv) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 50% AcOEtby 5% step), **5** was obtained in 63% yield as a colorless oil (377 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31–7.14 (m, 5H), 5.04 (s, 1H), 4.27–3.91 (m, 4H), 2.12 (s, 4H), 1.60 (s, 4H), 1.47 (d, J = 6.6 Hz, 3H), 1.31–1.13 (m, 15H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 31.49, 30.64; ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 127.8, 126.8, 126.6, 81.5 (d, J_{C-P} = 175.5 Hz), 75.8, 73.7, 61.7 (d, J_{C-P} = 57.4 Hz), 37.6, 36.4 (d, J_{C-P} = 4.4 Hz), 35.1, 29.8, 24.6, 22.2, 16.3 (t, J = 6.5 Hz); HRMS m/z (ESI) calcd for $C_{21}H_{37}NO_4P$ [M + H]$^+$ 398.2455, found 398.2452.

*Diethyl {1-[tert-Butyl(1-phenylethoxy)amino]cyclohexyl}-phosphonate (**6**).* CuBr (111.9 mg, 0.78 mmol, 0.55 equiv), Cu powder (99.1 mg, 1.56 mmol, 1.1 equiv), benzene (2 × 3 mL), N,N,N',N',N''-pentamethyldiethylenetriamine (0.16 mL, 0.78 mmol, 0.55 equiv), **6•** (435 mg, 1.42 mmol, 1 equiv), and bromoethylbenzene (288.7 mg, 1.56 mmol, 1.1 equiv) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 20% AcOEt by 3% step), **6** was obtained in 68% yield as a colorless oil (401 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28–7.16 (m, 5H), 4.87 (q, J = 6.5 Hz, 1H), 4.18–4.01 (m, 4H), 2.68–1.46 (m, 10H), 1.39 (d, J = 10.6 Hz, 3H), 1.33 (t, J = 7.0 Hz, 6H), 1.18 (s, 9H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 31.03; ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.6, 145.4, 127.9 (d, J_{C-P} = 33.4 Hz), 126.7, 126.2, 85.3 (d, J_{C-P} = 38.2 Hz), 68.1, 66.8, 64.0 (d, J_{C-P} = 52.1 Hz), 61.2 (d, J_{C-P} = 7.6 Hz), 33.9 (d, J_{C-P} = 54.5 Hz), 32.6 (d, J_{C-P} = 19.1 Hz), 30.2, 26.7, 25.1 (d, J_{C-P} = 57.8 Hz), 21.3, 16.5 (d, J_{C-P} = 6.0 Hz); HRMS m/z (ESI) calcd for $C_{22}H_{39}NO_4P$ [M + H]$^+$ 412.2611, found 412.2607.

*Benzyl 2-{[1-(Diethoxyphosphoryl)cyclopentyl](1-phenylethoxy)-amino}-2-methylpropanoate (**7**).* CuBr (57 mg, 0.40 mmol, 0.55 equiv), Cu powder (51 mg, 0.80 mmol, 1.1 equiv) N,N,N',N',N''-pentamethyldiethylenetriamine (83 μL, 0.40 mmol, 0.55 equiv), **7•** (300 mg, 0.73 mmol, 1 equiv), bromoethylbenzene (148 mg, 0.80 mmol, 1.1 equiv), and benzene (2 × 3 mL) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt), **7** was obtained in 80% as a colorless oil (301 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.22 (m, 10H), 5.03 (m, 3H), 4.02 (m, 4H), 2.06 (m, 4H), 1.39 (d, J = 6.5 Hz, 3H), 1.29 (m, 10H), 1.19 (m, 6H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 30.38; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 143.6, 136.1, 128.6, 128.2, 128.0, 127.3, 74.6, 68.3 (m), 66.5, 61.8 (m), 26.3, 25.1 (m), 21.7 (m), 16.6 (d, J_{C-P} = 3.8 Hz), 16.5 (d, J_{C-P} = 3.9 Hz); HRMS m/z (ESI) calcd for $C_{28}H_{41}NO_6P$ [M + H]$^+$ 518.2666, found 518.2665.

*Methyl 2-{[1-(Diethoxyphosphoryl)cyclohexyl](1-phenylethoxy)-amino}-2-methylpropanoate (**8**).* CuBr (193 mg, 1.35 mmol, 0.55

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equiv), Cu powder (172 mg, 2.70 mmol, 1.1 equiv), *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (282 μL, 1.35 mmol, 0.55 equiv), nitroxide **8•** (860 mg, 2.45 mmol, 1 equiv), bromoethylbenzene (499 mg, 2.7 mmol, 1.1 equiv), and benzene (2 × 3 mL) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt), **8** was obtained in 72% yield as a colorless oil (791 mg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 (m, 5H), 5.00 (q, *J* = 6.6 Hz, 1H), 4.07 (m, 4H), 3.61 (m, 3H), 2.47−0.92 (m, 22H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{31}P NMR (162 MHz, $CDCl_3$) δ 29.49; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.9, 144.7, 127.8, 126.9, 126.3, 82.9, 70.4, 68.1 (d, J_{C-P} = 136.3 Hz), 61.5 (d, J_{C-P} = 7.7 Hz), 61.4 (d, J_{C-P} = 7.7 Hz), 51.9, 32.8, 31.7, 26.32, 24.09, 21.34, 16.51 (d, J_{C-P} = 6.0 Hz); HRMS *m/z* (ESI) calcd for $C_{23}H_{39}NO_6P$ [M + H]$^+$ 456.2510, found 456.2513.

*Benzyl 2-{[1-(Diethoxyphosphoryl)cyclohexyl](1-phenylethoxy)-amino}-2-methylpropanoate (**9**).* CuBr (67 mg, 0.46 mmol, 0.55 equiv), Cu powder (59 mg, 0.93 mmol, 1.1 equiv), *N,N,N′,N′,N″*-pentamethyldiethylenetriamine (80 mg, 0.46 mmol, 0.55 equiv), nitroxide **9•** (360 mg, 0.84 mmol, 1 equiv), bromoethylbenzene (172 mg, 0.93 mmol, 1.1 equiv), and benzene (2 × 3 mL) were used. After flash chromatography (gradient, PE/AcOEt, from 0 to 100% AcOEt), **9** was obtained in 56% yield as a colorless oil (250 mg): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (m, 10H), 4.96 (m, 3H), 4.03 (m, 4H), 2.48−0.98 (m, 19H), 1.25 (t, *J* = 7.0 Hz, 3H), 1.20 (t, *J* = 7.0 Hz, 3H); ^{31}P NMR (121 MHz, $CDCl_3$) δ 29.51; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2, 144.7, 136.0, 128.6, 128.5, 128.1, 128.0, 127.8, 126.8, 126.2, 83.0, 70.6, 68.8, 67.2 (d, J_{C-P} = 5.7 Hz), 66.7, 61.4 (m), 26.5, 21.2, 16.5 (d, J_{C-P} = 5.9 Hz); HRMS *m/z* (ESI) calcd for $C_{29}H_{43}NO_6P$ [M + H]$^+$ 532.2823, found 532.2824.

Kinetic Measurements. Values of k_d' are measured by NMR and using **12•** as an alkyl radical scavenger as previously reported.[13] The evolution of alkoxyamine concentration is monitored, and the homolysis rate constant is given by eq 5. Activation energies (E_a) are determined using eq 6 and assuming the pre-exponential factor (*A*) equals 2.4×10^{14} s^{-1}.[21]

$$\ln \frac{[C]}{[C]_0} = -k_d t \quad (5)$$

$$k_d = 2.4 \times 10^{14} \times \exp\left(-\frac{E_a}{RT}\right) \quad (6)$$

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00541.

Physical characterizations of **7″**−**9″** and **3**−**9** (PDF)

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Notes

The authors declare no competing financial interest.

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(32) This relationship was developed only for the released phenethyl radical.
(33) $r_i(X)$ is the individual steric constant for group X, with i being the rank related to the value of $r(X)$, i.e., its size [the more negative $r(X)$ is, the larger X is].
(34) It is assumed that $a = b = 1$ and $\varepsilon = 0$ for the conventional steric effect and $a = b = 1$ and $\varepsilon = -E_s^B$ when the leveled steric effect occurs. Fragment **A** is in general ascribed to the fragment carrying either the largest group or the H atom at position β.
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(43) Only data reported in refs 20 and 24 are used. Data reported in other articles concern mainly cyclic nitroxides and do not significantly change the coefficients of eq 1.
(44) Because of the shift from sp^2 hybridization in the nitroxide to sp^3 hybridization in the alkoxyamine at the N atom, which is the major geometrical change occurring in the nitroxyl fragment, the angles change but the general arrangement around the nitroxyl moiety is not modified.
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(51) The leveled steric effect is also observed for alkoxyamines complying with item (i). In that case, E_s must be smaller than −6 and the nitroxyl fragment is either a large ring affording an easy change in conformation or a substituent that can change the steric fingerprint (Janus group). See refs 20, 24, and 50.

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