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Intramolecular Hydrogen Bond in Alkoxyamines. Influence on the C–ON Bond Homolysis

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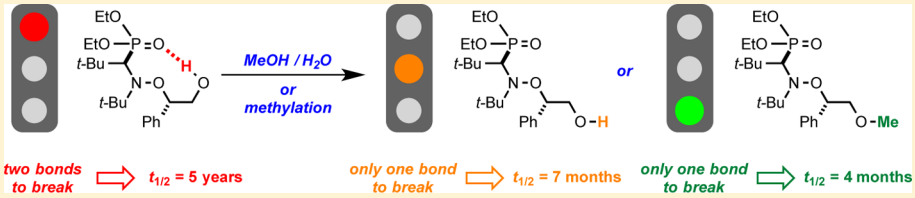
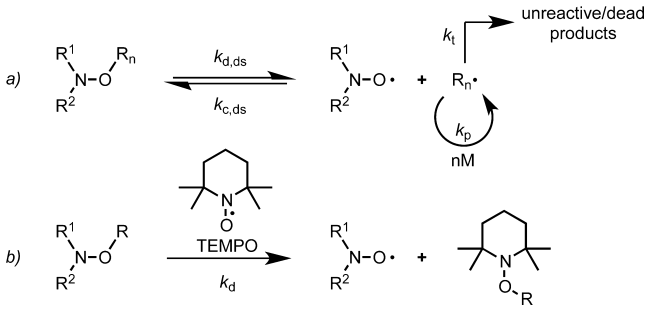
Supporting Information



ABSTRACT: The C–ON bond homolysis in alkoxyamines can be influenced by the presence of an intramolecular hydrogen bond (IHB) between the alkyl and the nitroxyl fragments, which leads to an 8-fold decrease in the homolysis rate constant k_d. When the IHB is disrupted by the solvent or by substitution of the hydrogen involved in the IHB by a protecting group (OMe, OAc, OBz, OBn, or OTBDMS), a higher homolysis rate constant k_d is observed, as expected from the correlations developed by Marque (Bertin, D.; Gigmes, D.; Marque, S.; Tordo, P. *Macromolecules* **2005**, *38*, 2638–2650). Results were confirmed by DFT calculations at the B3LYP/6-31G(d,p) level.

The high potential of alkoxyamines in nitroxide-mediated polymerization (NMP) has been revealed by Rizzardo[1] and Georges,[2] leading to the development of new materials (Scheme 1a).[3] Indeed, a (macro)alkoxyamine homolyzes to

Scheme 1. (a) Simplified Scheme for NMP; (b) Conditions To Investigate the C–ON Bond Homolysis in 2a–e



afford a nitroxide, which controls the polymerization, and an alkyl radical, which initiates ($k_{d,ds}$) and propagates (k_p) the polymerization. The presence of nitroxide favors the reformation of the alkoxyamine ($k_{c,ds}$), keeping the dead products at such low level that the polymerization is considered as *pseudoliving*.[4] This new type of controlled polymerization has generated a tremendous amount of work on the kinetics of this process.[3,4] It appears that the homolysis, i.e., the main process, is ruled by various factors such as steric, polar, and stabilization effects.[4]

As far as we know, only a few investigations on the effect of the intramolecular hydrogen bond (IHB) have been carried out by Marque,[5−7] Matyjaszewski,[8] Studer,[5,9] and Hawker.[10] All were dealing with the IHB in the released nitroxide, implying an increase in k_d. However, to the best of our knowledge, so far, no IHB between the alkyl and the nitroxyl fragments has been reported. The existence of an IHB in alkoxyamine **1** has been claimed,[11,12] but no clear evidence has been given so far.[13]

Interested in the consequences of the existence of an IHB between the alkyl and the nitroxyl fragments of an alkoxyamine and following our ongoing program of synthesis and characterization of new functionalizable or chemically–activatable alkoxyamines,[14−20] we propose herein a new alkoxyamine **2a**, carrying an alcohol function on the alkyl fragment that presents an IHB strikingly influencing the C–ON bond homolysis as well as several derivatives **2b–f** (Figure 1)

Alkoxyamine **2a** was synthesized from **SG1** nitroxide (*N*-(2-methylpropyl)-*N*-(1-diethylphosphono-2,2-dimethylpropyl)-*N*-oxyl) and 2-bromo-2-phenylethanol using Matyjaszewski's procedure,[21] affording **2a** in a 1.5:1 mixture of diastereoisomers which were separated by purification on silica gel (see the Supporting Information). Prompted by an abnormalous ^{31}P

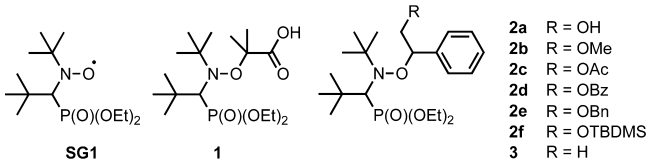


Figure 1. Structures of SG1 nitroxide and alkoxyamines **1**, **2a–f**, and **3**.

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chemical shift for the major diastereoisomer (δ = 27.7 ppm in $CDCl_3$, compared to δ = 23.6 ppm for the minor diastereoisomer[22]), we first investigated the ^{31}P chemical shifts for both diastereoisomers in several deuterated solvents (Table 1). The differences in chemical shift between the diastereoisomers $\Delta\delta_P$ are split in three families: $\Delta\delta_P$ < 3 for solvents known to disrupt IHB DMSO-d_6, DMF-d_7, MeOH-d_4/D_2O); 3 < $\Delta\delta_P$ < 3.5 for solvents known to disfavor IHB (MeOH-d_4, acetonitrile-d_3, acetone-d_6), and $\Delta\delta_P$ > 3.5 for solvents favoring IHB (benzene-d_6, chloroform-d_1). However, these differences did not afford a clear-cut on the existence of IHB, as the minor diastereoisomer experienced a stronger solvent effect ($\Delta'\delta_P$ = 1.82 ppm) than the major diastereoisomer ($\Delta'\delta_P$ = 1.13 ppm).

Table 1. Evolution of the ^{31}P Chemical Shifts for the Diastereoisomers of Alkoxyamine 2a in Several Deuterated Solvents[a]

NMR solvent	δ_P for *SR/RS*-**2a**[b]	δ_P for *SS/RR*-**2a**[b]	$\Delta\delta_P$
DMSO-d_6	27.14	24.56	2.58
MeOH-d_4/D_2O[c]	28.26	25.43	2.83
DMF-d_7	27.27	24.42	2.85
MeOH-d_4	28.19	25.12	3.07
acetonitrile-d_3	27.77	24.47	3.30
acetone-d_6	27.90	24.59	3.31
benzene-d_6	27.44	23.76	3.68
chloroform-d_1	27.74	23.62	4.12

[a] 85% H_3PO_4 was used as internal reference (δ_P = 0 ppm). [b] *RS/SR*-**2a** is the major diastereoisomer, and *SS/RR*-**2a** the minor one (vide infra). [c] *v*/*v* 1:1.

$^1H-^{31}P$ HOESY experiments were then performed on each diastereoisomer and strong correlations between the hydrogen atom of the alcohol function and the phosphorus atom were observed only for the major diastereoisomer of alkoxyamine **2a** (Figure 2a and Supporting Information).

IR spectra were then recorded in CCl_4 at several concentrations (0.2 M to 2 μM) for each diastereoisomer, and despite the use of low concentrations, the wavenumber n_{OH} was almost constant for the major diastereoisomer, while it rapidly decreased when the concentration in the minor diastereoisomer increased (Figure 2b,c and the Supporting Information). Such behavior is a characteristic of an intermolecular hydrogen bond for the minor diastereoisomer of **2a** and an IHB for the major diastereoisomer of **2a**. Ultimately, recrystallization of each diastereoisomer afforded single crystals suitable for X-ray diffraction (Figure 3). The crystals of the minor *SS/RR* diastereoisomer showed the occurrence of an intermolecular hydrogen bond between the OH and the O=P functions, while an IHB was observed in the major *SR/RS* diastereoisomer between the OH and the O=P functions, leading to a pseudo 9-membered ring and thus confirming the ^{31}P NMR and IR observations. This latter IHB has a length of 1.92 Å and the O–H---O(=P) angle is 177.1°, in the expected range for strong IHB.[23,24]

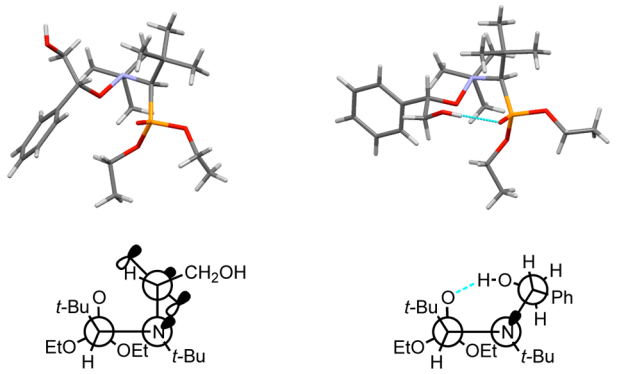
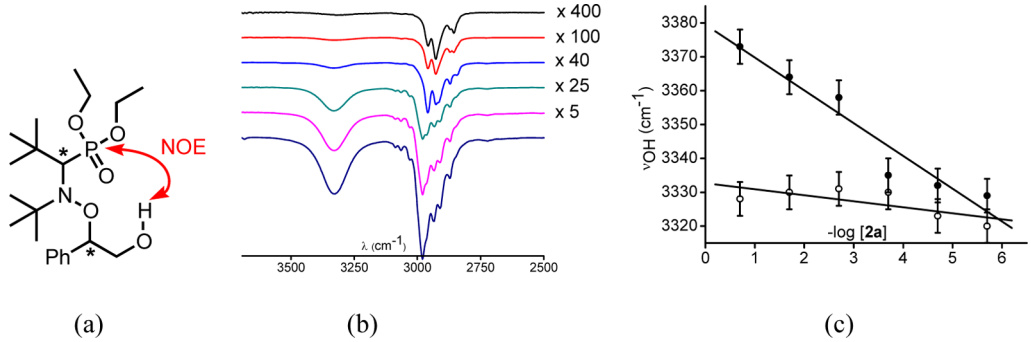


Figure 3. Top: ORTEP view of *SS/RR*-**2a** (left) and *SR/RS*-**2a** (right). Bottom: corresponding Newman projections. The IHB is shown in turquoise-blue.

In order to investigate the influence of this hydrogen bond on the C–ON bond homolysis, a series of derivatives of alkoxyamine **2a** was synthesized using several protecting groups for the alcohol function: a small one (Me, **2b**), electron-withdrawing ones (Ac, **2c**; Bz, **2d**), as well as hindered ones (Bn, **2e**; TBDMS, **2f**). Both diastereoisomers of alkoxyamines **2b** and **2c**, and only the *RR/SS* diastereoisomer of alkoxyamine **2d** are crystalline and were obtained as single crystals in order to be also analyzed by X-ray diffraction (see the Supporting Information).[25] Other compounds were obtained as oils. Rate constants were measured as previously described using 2 equiv of TEMPO as alkyl radical scavenger in *tert*-butylbenzene (*t*-BuPh) as solvent (Scheme 1b).[26] The activation energies E_a of each reaction (Table 1) were estimated using the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1}.[27] The homolysis rate constant of diastereoisomers of alkoxyamine **2a** was also measured in MeOH/H_2O (v/v 1:1) and in DMSO in order to investigate the stability of the IHB.



(a) (b) (c)

Figure 2. (a) Selected $^1H-^{31}P$ HOESY correlations observed for *SR/RS*-**2a**. (b) FTIR spectra covering the C–H and O–H bands for concentrations of 0.2 M (navy), 0.02 M (magenta), 2 mM (green), 0.2 mM (blue), 0.02 mM (red), and 2 μM (black) in CCl_4 for *SR/RS*-**2a**. (c) Plot ν_{OH} vs –log [**2a**] for the *SR/RS*- (○) and *SS/RR*- (●) diastereoisomers of **2a** from 0.2 M to 2 μM in CCl_4.

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Table 2. Experimental Temperature (°C) and C−ON Bond Homolysis Rate Constants k_d, Activation Energies E_a, Re-estimated Rate Constants k'_d for the Minor *SS*/*RR*- and the Major *RS*/*SR*-Diastereoisomers of Alkoxyamines 2a−f and Ratio of the Re-estimated Rate Constants, in *t*-BuPh as Solvent unless Mentioned

		k_d (10^{-3} s^{-1})[a]		E_a (kJ/mol)[b]		k'_d (10^{-3} s^{-1})[c]		
	temp (°C)	*RS*/*SR*	*RR*/*SS*	*RS*/*SR*	*RR*/*SS*	*RS*/*SR*	*RR*/*SS*	r[d]
2a	103.5	0.23	1.82	129.9	123.4	1.31	9.52	7.3
2a[e]	91.0	0.34	0.71	124.4	122.2	7.05	13.9	2.0
2a[f]	82.0	0.08	0.30	125.5	121.7	5.00	16.2	3.2
2b	101.0	1.53	2.19	123.2	122.1	10.4	14.6	1.4
2c	101.0	1.22	1.60	123.9	123.0	8.36	10.8	1.3
2d	101.0	1.32	2.60	123.6	121.5	9.01	17.2	1.9
2e	101.0	0.57	1.06	126.2	124.3	4.05	7.31	1.8
2f	121.0	3.44	4.65	127.1	126.1	3.12	4.22	1.4
3[g]	98.0	0.85	0.79	124.0	124.2	8.05	7.51	0.9

[a]Measured at the experimental temperature. Each reported value is the average of two runs. Statistical error is less than 2%. For all reported values, the error is lower than 5% and is mainly due to discrepancies in the temperature measurements. [b]Activation energy E_a estimated applying the averaged frequency factor $A = 2.4 \times 10^{14}$ s^{-1} (see ref 27). Error was given as ±1 kJ/mol. [c]k'_d values estimated at 120 °C using the E_a values given in the fifth and sixth columns and $A = 2.4 \times 10^{14}$ s^{-1}. [d]$r = k'_{d,RR/SS}/k'_{d,RS/SR}$ at 120 °C. [e]In MeOH/H_2O (v/v 1:1). [f]In DMSO. [g]Values are from ref 26.

By comparing the data for alkoxyamine **3**, which carries a styryl derivative and whose diastereoisomers have similar activation energies, and the r values for **2b−f**, no significant structural effects were observed, as already reported for other alkoxyamines.[27,28] Concerning alkoxyamine **2a**, it is clear that the IHB has a striking influence on the homolysis rate, leading to a 7-fold decrease in k_d, which corresponds to a 6.5 kJ/mol increase in the activation energy E_a of *RS*/*SR*-**2a** compared to *RR*/*SS*-**2a**. The IHB is clearly responsible for the decrease in the homolysis rate constant for *RS*/*SR*-**2a**, as two bonds must be broken instead of only one.[29] When switching from *t*-BuPh to MeOH/H_2O (v/v 1:1) or DMSO, the difference in E_a between the two diastereoisomers of **2a** was reduced to 2.2 and 3.8 kJ/mol, respectively. This demonstrated that, despite the solvent effect, the IHB can have a striking impact on the homolysis rate as the use of a polar solvent disrupts the IHB and can therefore restore similar k_d values for the diastereoisomers of **2a**.

The homolysis rates contants k_d predicted by using the correlations developed by Marque[27] afforded activation energy values that were close to the experimental values for the *RR*/*SS* diastereoisomer, i.e., 121.0, 121.0, 119.6, 118.0, 121.0, and 125.5 for alkoxyamines **2a**, **2b**, **2c**, **2d**, **2e**, and **2f**, respectively, keeping in mind that several parameters needed to be estimated or assumed.[30] On the other hand, the 8.9 kJ/mol difference in activation energies between experimental and predicted values for the *RS*/*SR* diastereoisomer of **2a** also denotes the effect of IHB on the strenghtening of the C−ON bond.

To gain deeper insight into the various effects involved in the chemical triggering of the C−ON bond homolysis in alkoxyamines, calculations were performed, using the B3LYP/6-31G(d,p) method, to optimize the geometries and to determine NBO interactions.[16] Calculations were performed on each diastereoisomers of alkoxyamines **2a** and **2b** and showed that *RR*/*SS*-**2a** and *RR*/*SS*-**2b** displayed the same conformation, while *RS*/*SR*-**2a** presented a less eclipsed conformation than *RS*/*SR*-**2b**, allowing the formation of the IHB (see Figure 3). As already reported, no correlation was found between the geometric parameters of the reactive center (l_{C13-O1}, l_{N2-O1}, d_{C13-N2}, and $\alpha_{N2O1C13}$ in Table 1, Supporting Information) and the k_d of the alkoxyamines. The calculated homolysis enthalpies are in good agreement with the observed reactivity; i.e., $\Delta\Delta_rH$ is significant between *RS*/*SR*-**2a** and *RR*/*SS*-**2a** ($\Delta\Delta_rH$ = 30.7 kJ/mol), which corresponds to the influence of the IHB in *RS*/*SR*-**2a**. As expected, it is smaller between *RS*/*SR*-**2b** and *RR*/*SS*-**2b** ($\Delta\Delta_rH$ = 4.6 kJ/mol), where IHB is no longer present. NBO calculations were also performed on *RS*/*SR*-**2a** and the interaction between the OH, and the P═O group was evaluated as 42.1 kJ/mol (Figure 4). This stabilization led to $k_{d,RS/SR\text{-}2b} \approx 8 \times k_{d,RS/SR\text{-}2a}$.

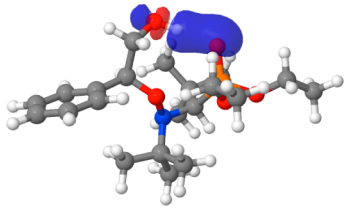

Figure 4. NBO view of the IHB bond ($n_{P=O} \rightarrow \sigma_{O-H}^*$) for alkoxyamine *RS*/*SR*-**2a**.

During the homolysis, a $\pi_{Ph} \rightarrow \sigma_{C-ON}^*$ interaction took place in the transition state.[33] The differences observed in the dihedral angle <O1C13C16C17> are in agreement with the interaction energies calculated by NBO (see the Supporting Information) but have no effect on the homolysis rates.

In conclusion, we have demonstrated that the polar, steric, and stabilization effects, which rule the C−ON bond homolysis in alkoxyamines, can be greatly influenced and even counterbalanced by the effect of an IHB. As an example, the half-life time at 25 °C of *RS*/*SR*-**2a** is 5 years in *t*-BuPh, while it is shortened to only 7 months when switching to MeOH/H_2O (v/v 1:1) where the IHB is disrupted and to only 4 months after methylation (for *RS*/*SR*-**2b**).[34] These facts are interesting, as their activation energy, and therefore their stability, can be adjusted by chemical activation and/or by changing the solvent (loss of IHB).

■ EXPERIMENTAL SECTION

General Experimental Methods. All corresponding glassware was oven-dried (80 °C) and/or carefully dried in line with a flameless heat gun. All solvents were used as received. Routine monitoring of reactions was performed using silica gel 60 F_{254}, aluminum-supported TLC plates; spots were visualized using UV light and ethanolic acidic *p*-anisaldehyde solution or ethanolic phosphomolybdic solution, followed by heating. Purifications by means of column chromatog-

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raphy were performed with silica gel 60 (230−400 mesh) and gradients of Et_2O/pentane, AcOEt/pentane, acetone/pentane, or MeOH/CH_2Cl_2. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded in $CDCl_3$ or C_6D_6 solutions on 300 or 400 MHz spectrometers. Chemical shifts (δ) in ppm are reported using residual nondeuterated solvents as internal reference; min and Maj stand for minor and major diastereoisomers, respectively. High-resolution mass spectra (HRMS) have been performed using a mass spectrometer equipped with pneumatically assisted atmospheric pressure ionization. The sample was ionized in positive mode electrospray in the following conditions: electrospray voltage (ISV): 5500 V; orifice voltage (OR): 80 V; nebulizing gas flow pressure (air): 20 psi. The mass spectrum was obtained using a time-of-flight analyzer (ToF). The measure was realized in triplicate, with double internal standardization. The sample was dissolved in CH_2Cl_2 (400 μL) then diluted (dilution factor $1/10^4$) in a methanolic solution of ammonium acetate (3 mM). The sample solution was infused in the ionization source at a 10 μL/min flow rate.

Diethyl (1-(*tert*-Butyl(2-hydroxy-1-phenylethoxy)amino)-2,2-dimethylpropyl)phosphonate (2a). To a stirred suspension of CuBr (1.34 g, 9.35 mmol, 0.55 equiv) and metallic Cu (1.19 g, 18.7 mmol, 1.1 equiv) in degassed benzene (40 mL) was added *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (2.00 mL, 9.35 mmol, 0.55 equiv). The resulting mixture was stirred under argon at room temperature for 30 min, and then a solution of 2-bromo-2-phenylethan-1-ol[36] (3.76 g, 18.7 mmol, 1.1 equiv) and SG1 (5.00 g, 17.0 mmol, 1.0 equiv) in degassed benzene (40 mL) was slowly added. The mixture was stirred under argon at room temperature for 12 h. It was then diluted with ethyl acetate, filtered, and washed several times with saturated aqueous ammonia solution, water, and brine. After drying with Na_2SO_4, filtration, and concentration in vacuo, column chromatography on silica gel gave **2a** (6.36 g, 90%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). An aliquot of **2a** was further separated to give pure diastereoisomers *RS*/*SR*-**2a** (white crystals) and *SS*/*RR*-**2a** (white crystals) for full characterization. *RS*/*SR*-**2a**: mp = 99−101 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.35−7.21 (m, 5H), 6.13 (br s, 1H), 5.02 (dd, *J* = 6.2, 2.4 Hz, 1H), 4.53−4.39 (m, 1H), 4.34−4.21 (m, 1H), 4.20−4.08 (m, 1H), 4.08−3.96 (m, 1H), 3.92 (dd, *J* = 13.1, 2.4 Hz, 1H), 3.76 (dd, *J* = 13.1, 6.2 Hz, 1H), 3.46 (d, *J* = 27.7 Hz, 1H), 1.39 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H) 1.28 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 141.3, 128.1, 127.4, 127.3, 90.8, 69.2 (d, *J* = 139.2 Hz), 66.5, 62.0 (d, *J* = 6.7 Hz), 61.8, 59.7 (d, *J* = 7.6 Hz), 35.7 (d, *J* = 5.4 Hz), 30.8 (d, *J* = 5.8 Hz), 28.5, 16.6 (d, *J* = 5.6 Hz), 16.2 (d, *J* = 6.9 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 27.0; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}N_1O_5P_1$ $[M + H]^+$ 416.2560, found 416.2561. *SS*/*RR*-**2a**: mp = 84−85 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.44−7.39 (m, 2H), 7.32−7.21 (m, 3H), 5.50 (dd, *J* = 8.8, 3.7 Hz, 1H), 4.53 (br s, 1H), 4.33 (dd, *J* = 11.9, 8.8 Hz, 1H), 4.02−3.78 (m, 2H), 3.78 (dd, *J* = 11.9, 3.7 Hz, 1H), 3.43 (d, *J* = 25.7 Hz, 1H), 3.36−3.13 (m, 2H), 1.31 (s, 9H), 1.28 (s, 9H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 138.4, 128.4, 128.3, 128.2, 81.8, 71.2 (d, *J* = 141.8 Hz), 68.2, 62.9, 61.8 (d, *J* = 6.5 Hz), 59.1 (d, *J* = 7.4 Hz), 35.5 (d, *J* = 4.3 Hz), 31.0 (d, *J* = 6.1 Hz), 27.9, 16.5 (d, *J* = 5.6 Hz), 16.3 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 22.9; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}N_1O_5P_1$ $[M + H]^+$ 416.2560, found 416.2564.

Diethyl (1-(*tert*-Butyl(2-methoxy-1-phenylethoxy)amino)-2,2-dimethylpropyl)phosphonate (2b). To an ice-cold stirred solution of **2a** (500 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (12 mL) under argon was added *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine (772 mg, 3.60 mmol, 3.0 equiv) followed by trimethyloxonium tetrafluoroborate (262 mg, 1.80 mmol, 1.5 equiv). The mixture was stirred under argon at room temperature for 12 h, and then it was quenched with aqueous 1 M hydrochloric acid. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave **2b** (425 mg, 82%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). An aliquot of **2b** was further separated to give pure diastereoisomers *RS*/*SR*-**2b** (white crystals) and *SS*/*RR*-**2b** (white crystals) for full characterization. *RS*/*SR*-**2b**: mp = 102−103 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.31−7.18 (m, 5H), 4.90 (dd, *J* = 3.7, 9.0 Hz, 1H), 4.40−4.18 (m, 2H), 4.16−3.86 (m, 3H), 3.63 (t, *J* = 9.2 Hz, 1H), 3.30 (d, *J* = 26.2 Hz, 1H), 3.16 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.20 (s, 9H), 0.83 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.3, 128.1, 128.0, 127.4, 88.2, 75.5, 69.7 (d, *J* = 138.2 Hz), 61.7 (d, *J* = 6.3 Hz), 61.6, 59.0, 58.9 (d, *J* = 6.9 Hz), 35.9 (d, *J* = 5.7 Hz), 30.0 (d, *J* = 5.9 Hz), 28.7, 16.9 (d, *J* = 5.3 Hz), 16.4 (d, *J* = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 25.0; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{41}N_1O_5P_1$ $[M + H]^+$ 430.2717, found 430.2718. *SS*/*RR*-**2b**: mp = 79−80 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.50−7.46 (m, 2H), 7.31−7.21 (m, 3H), 5.20 (dd, *J* = 3.2, 8.9 Hz, 1H), 4.22 (dd, *J* = 3.3, 8.9 Hz, 1H), 4.00−3.90 (m, 1H), 3.89−3.79 (m, 1H), 3.73 (t, *J* = 8.9 Hz, 1H), 3.44−3.31 (m, 1H), 3.40 (d, *J* = 26.4 Hz), 3.30−3.19 (m, 1H), 3.24 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.21 (s, 9H), 1.20 (s, 9H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.4, 128.8, 127.8, 127.7, 80.7, 74.0, 69.9 (d, *J* = 139.4 Hz), 61.7, 61.6 (d, *J* = 6.4 Hz), 59.4, 58.7 (d, *J* = 7.5 Hz), 35.4 (d, *J* = 4.9 Hz), 30.8 (d, *J* = 5.9 Hz), 28.0, 16.4 (d, *J* = 5.7 Hz), 16.2 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 23.7; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{41}N_1O_5P_1$ $[M + H]^+$ 430.2717, found 430.2717.

2-((*tert*-Butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)-amino)oxy)-2-phenylethyl acetate 2c. To an ice-cold stirred solution of **2a** (500 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added under argon pyridine (6 mL) followed by acetic anhydride (170 mL, 1.80 mmol, 1.5 equiv) and a catalytic amount of *N*,*N*-dimethylaminopyridine. The mixture was stirred under argon at room temperature for 12 h, and then it was quenched with aqueous 1 M hydrochloric acid. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave **2c** (485 mg, 88%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). An aliquot of **2c** was further separated to give pure diastereoisomers *RS*/*SR*-**2c** (white crystals) and *SS*/*RR*-**2c** (white crystals) for full characterization. *RS*/*SR*-**2c**: mp = 82−83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.33−7.23 (s, 5H), 5.09 (dd, *J* = 8.1, 3.9 Hz, 1H), 4.84 (dd, *J* = 10.9, 3.9 Hz, 1H), 4.48 (dd, *J* = 10.9, 8.1 Hz, 1H), 4.43−4.4.35 (m, 1H), 4.20−4.05 (m, 2H), 4.04−3.94 (m, 1H), 3.35 (d, *J* = 26.3 Hz, 1H), 1.80 (s, 3H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.24 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 169.5, 140.0, 127.4, 127.3, 127.0, 86.4, 69.8 (d, *J* = 139.0 Hz), 65.7, 61.1, 61.0 (d, *J* = 6.1 Hz), 58.5 (d, *J* = 7.6 Hz), 35.2 (d, *J* = 5.4 Hz), 29.5 (d, *J* = 5.6 Hz), 28.0, 20.1, 16.3 (d, *J* = 5.4 Hz), 15.7 (d, *J* = 6.7 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 24.6; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{41}N_1O_6P_1$ $[M + H]^+$ 458.2666, found 458.2664. *SS*/*RR*-**2c**: mp = 78−79 °C; ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39−7.30 (m, 2H), 7.20−7.09 (m, 3H), 5.19 (dd, *J* = 8.3, 3.3 Hz, 1H), 4.70 (dd, *J* = 10.5, 3.3 Hz, 1H), 4.38 (dd, *J* = 10.5, 8.3 Hz, 1H), 3.89−3.70 (m, 2H), 3.34−3.10 (m, 2H), 3.32 (d, *J* = 26.5 Hz, 1H), 1.77 (s, 3H), 1.18−1.06 (m, 21H), 0.79 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.2, 138.7, 128.4, 127.7, 127.5, 79.5, 69.4 (d, *J* = 139.4 Hz), 64.5, 61.6, 61.3 (d, *J* = 6.5 Hz), 58.6 (d, *J* = 7.4 Hz), 35.0 (d, *J* = 4.7 Hz), 30.5 (d, *J* = 6.0 Hz), 27.6, 20.5, 16.1 (d, *J* = 5.6 Hz), 15.9 (d, *J* = 7.0 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 23.4; HRMS (ESI) *m*/*z* calcd for $C_{23}H_{41}N_1O_6P_1$ $[M + H]^+$ 458.2666, found 458.2661.

2-((*tert*-Butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)-amino)oxy)-2-phenylethyl Benzoate (2d). To an ice-cold stirred solution of **2a** (500 mg, 1.20 mmol, 1.0 equiv) in CH_2Cl_2 (6 mL) was added under argon pyridine (6 mL) followed by benzoyl chloride (210 mL, 1.80 mmol, 1.5 equiv) and a catalytic amount of *N*,*N*-dimethylaminopyridine. The mixture was stirred under argon at room temperature for 12 h, and then it was quenched with aqueous 1 M hydrochloric acid. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave **2d** (535 mg, 85%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). An aliquot of **2d** was further separated to give pure diastereoisomers *RS*/*SR*-**2d** (colorless oil) and *SS*/*RR*-**2d**

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(white crystals) for full characterization. *RS*/*SR*-**2d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.80−7.73 (m, 2H), 7.41−7.19 (m, 8H), 5.23 (dd, *J* = 8.2, 3.9 Hz, 1H), 5.11 (dd, *J* = 10.7, 3.9 Hz, 1H), 4.68 (dd, *J* = 10.7, 8.2 Hz, 1H), 4.46−3.32 (m, 1H), 4.26−3.94 (m, 3H), 3.39 (d, *J* = 26.3 Hz, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.27 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 165.9, 140.8, 132.7, 130.4, 129.5, 128.2, 128.1, 128.0, 127.7, 87.1, 69.5 (d, *J* = 140.0 Hz), 67.1, 61.9, 61.8 (d, *J* = 6.0 Hz), 59.4 (d, *J* = 6.8 Hz), 35.9 (d, *J* = 5.3 Hz), 30.2 (d, *J* = 5.3 Hz), 28.7, 16.8 (d, *J* = 5.5 Hz), 16.4 (d, *J* = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 24.7; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{43}N_1O_6P_1$ $[M + H]^+$ 520.2823, found 520.2825. *SS*/*RR*-**2d**: mp = 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.88−7.83 (m, 2H), 7.55−7.43 (m, 3H), 7.38−7.19 (m, 5H), 5.46 (dd, *J* = 7.8, 3.4 Hz, 1H), 5.02 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.73 (dd, *J* = 10.8, 7.8 Hz, 1H), 4.03−3.80 (m, 2H), 3.49−3.28 (m, 1H), 3.45 (d, *J* = 26.6 Hz, 1H), 1.25 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H, partially overlapped), 1.22 (s, 9H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 166.3, 139.2, 132.8, 130.2, 129.6, 128.6, 128.3, 128.0, 127.9, 80.0, 69.8 (d, *J* = 139.3 Hz), 65.5, 62.0, 61.7 (d, *J* = 6.5 Hz), 59.0 (d, *J* = 7.4 Hz), 35.4 (d, *J* = 4.5 Hz), 30.9 (d, *J* = 6.0 Hz), 28.0, 16.4 (d, *J* = 5.6 Hz), 16.3 (d, *J* = 6.8 Hz); ^{31}P NMR (162 MHz, $CDCl_3$) δ = 23.5; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{43}N_1O_6P_1$ $[M + H]^+$ 520.2823, found 520.2821.

Diethyl (1-((2-(Benzyloxy)-1-phenylethoxy)-*tert*-butylamino)-2,2-dimethylpropyl) Phosphonate (2e). To a stirred solution of **2a** (500 mg, 1.20 mmol, 1.0 equiv) in THF (12 mL) was added NaH (60% in mineral oil, 72 mg, 1.80 mmol, 1.5 equiv). The mixture was stirred under argon atmosphere at 0 °C for 30 min, and then benzyl bromide (430 mL, 3.60 mmol, 3.0 equiv) and a catalytic amount of tetrabutylammonium iodide were added. After the mixture was stirred at room temperature for 12 h, it was quenched with aqueous 1 M hydrochloric acid. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave **2e** (395 mg, 65%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). Diastereoisomers *RS*/*SR*-**2d** and *SS*/*RR*-**2d** could not be separated and were obtained as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53−7.04 (m, 10H, Maj + min), 5.27 (dd, *J* = 8.7, 3.2 Hz, 1H, min), 5.02 (dd, *J* = 8.2, 3.4 Hz, 1H, Maj), 4.47−4.29 (m, 4H Maj + min), 4.17−3.73 (m, 4H, Maj + min), 3.38 (d, *J* = 26.4 Hz, 1H, min), 3.35 (d, *J* = 26.1 Hz, 1H, Maj), 1.33−1.16 (m, 15H, Maj + min), 0.91 (br s, 9H, Maj + min); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.2 (Maj), 140.4 (min), 138.8 (Maj), 138.4 (min), 128.8 (min), 128.1 (min), 128.0 (Maj), 127.9 (Maj), 127.8 (Maj), 127.7 (min), 127.6 (min), 127.5 (Maj), 127.3 (min), 127.2 (Maj), 127.1 (min), 127.0 (Maj), 88.5 (Maj), 81.0 (min), 73.3 (Maj), 73.1 (min), 72.6 (Maj), 71.2 (min), 69.8 (d, *J* = 139.1 Hz, min), 69.6 (d, *J* = 138.8 Hz, Maj), 61.7−61.5 (m, Maj + min), 58.8 (d, *J* = 7.4 Hz, Maj), 58.7 (d, *J* = 7.3 Hz, min), 35.8 (d, *J* = 5.8 Hz, Maj), 35.3 (d, *J* = 4.9 Hz, min), 30.8 (d, *J* = 6.0 Hz, min), 30.0 (d, *J* = 5.8 Hz, Maj), 28.6 (Maj), 27.9 (min), 16.8 (d, *J* = 5.1 Hz, Maj), 16.4−16.1 (Maj + min); ^{31}P NMR (162 MHz, $CDCl_3$): δ = 25.1, 23.8; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{45}N_1O_5P_1$ $[M + H]^+$ 506.3030, found 506.3032.

Diethyl (8-*tert*-Butyl-2,2,3,3,10,10-hexamethyl-6-phenyl-4,7-dioxa-8-aza-3-silaundecan-9-yl)phosphonate (2f). To an ice-cold stirred solution of **2a** (500 mg, 1.20 mmol, 1.0 equiv) in DMF (12 mL) was added under argon imidazole (245 mg, 3.60 mmol, 3.0 equiv) followed by *tert*-butyldimethylsilyl chloride (272 mg, 1.80 mmol, 1.5 equiv). The mixture was stirred under argon at room temperature for 12 h, and then it was quenched with aqueous 1 M hydrochloric acid. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2. The organic phases were combined, washed with saturated aqueous $NaHCO_3$ solution, water, and brine, dried with Na_2SO_4, and concentrated in vacuo. Column chromatography on silica gel gave **2f** (580 mg, 91%) as a 1.5:1 mixture of diastereoisomers (NMR ratio). An aliquot of **2f** was further separated to give pure diastereoisomers *RS*/*SR*-**2f** (colorless oil) and *SS*/*RR*-**2f** (colorless oil) for full characterization. *RS*/*SR*-**2f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.30−7.15 (m, 5H), 4.83 (dd, *J* = 8.9, 3.7 Hz, 1H), 4.46−4.28 (m, 2H), 4.19−3.90 (m, 3H), 3.74 (t, *J* = 8.9 Hz, 1H), 3.33 (d, *J* = 26.1 Hz, 1H), 1.34 (t, *J* = 7.0 Hz, 3H), 1.22 (s, 9H), 0.90 (s, 9H), 1.28 (t, *J* = 7.0 Hz, 3H), 0.69 (s, 9H), −0.21 (s, 3H), −0.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.7, 128.2, 127.6, 126.9, 90.5, 69.4 (d, *J* = 138.4 Hz), 66.4, 61.7 (d, *J* = 6.3 Hz), 61.6, 58.9 (d, *J* = 7.4 Hz), 35.9 (d, *J* = 5.7 Hz), 30.0 (d, *J* = 5.6 Hz), 28.8, 25.8, 18.2, 16.90 (d, *J* = 5.4 Hz), 16.4 (d, *J* = 6.9 Hz), −5.6, −5.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 25.2; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{53}N_1O_5P_1Si_1$ $[M + H]^+$ 530.3425, found 530.3420. *SS*/*RR*-**2f**: ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43−7.39 (m, 2H), 7.26−7.16 (m, 3H), 5.08 (dd, *J* = 7.6, 3.4 Hz, 1H), 4.28 (dd, *J* = 9.5, 3.4 Hz, 1H), 3.99−3.79 (m, 3H), 3.48−3.33 (m, 2H), 3.41 (d, *J* = 26.5 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H), 1.21 (s, 9H), 1.19 (s, 9H), 0.92 (t, *J* = 7.1 Hz, 3H), 0.75 (s, 9H), −0.19 (s, 3H), −0.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.7, 128.9, 127.4, 127.3, 83.0, 69.8 (d, *J* = 139.0 Hz), 64.3, 61.8 (d, *J* = 6.2 Hz), 61.7, 58.9 (d, *J* = 7.5 Hz), 35.4 (d, *J* = 4.8 Hz), 30.9 (d, *J* = 6.0 Hz), 28.1, 25.8, 18.2, 16.5 (d, *J* = 6.0 Hz), 16.3 (d, *J* = 6.9 Hz), −5.7; ^{31}P NMR (162 MHz, $CDCl_3$) δ = 23.9; HRMS (ESI) *m*/*z* calcd for $C_{27}H_{53}N_1O_5P_1Si_1$ $[M + H]^+$ 530.3425, found 530.3416.

■ ASSOCIATED CONTENT

Supporting Information

Characterization of alkoxyamines **2a**−**f** (^{1}H and ^{13}C NMR spectra, IR spectra, ^{1}H−^{31}P HOESY spectra and CIF files), kinetic measurements, and calculation details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(25) X-ray crystallographic data: CCDC 930683 (*RS*/*SR*-**2a**); CCDC 930684 (*SS*/*RR*-**2a**); CCDC 930686 (*RS*/*SR*-**2b**); CCDC 930685 (*SS*/*RR*-**2b**); CCDC 930681 (*RS*/*SR*-**2c**); CCDC 930680 (*SS*/*RR*-**2c**); CCDC 930682 (*SS*/*RR*-**2d**); These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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(29) As underlined by one of the reviewers, a major part of the stabilizing effect of the IHB might be necessary to bring the alkoxyamine into this comparably unfavorable conformation.
(30) E_a values were estimated with eq 31 given in ref 27. In virtue of the Minimal Steric Interaction Principle,[31] the bulkiness of $PhCHCH_2$-R was assumed to be as high as for $PhCHCH_3$, i.e., $\upsilon = 0.86$. It was assumed that the effect of R (Figure 1) was not significant, and consequently, the radical stabilization constant $\sigma_{RS,\ R} \approx \sigma_{RS,\ PhCHCH3} = 0.34$. Electrical constants σ_I were assumed using eqs 10 and 11 in ref 27: $\sigma_{I,CH2OH} = 0.11$ and assuming $\sigma_{CH2OBn} \approx \sigma_{CH2OMe}$, see ref 32; $\sigma_{I,CHCH2OAc} = 0.08$ with $\sigma_{I,CH2OAc} = 0.15$; $\sigma_{I,PhCHCH2OBz} = 0.09$ with $\sigma_{I,PhCOO} = 0.43$; $\sigma_{I,PhCHCH2OTBDMS} = 0.04$ assuming $\sigma_{CH2OTBDMS} = \sigma_{CH2OSiMe3} = 0$ and $F_{CH2OSiMe3} = 0$.
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