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Direct functionalization of labile alkoxyamines

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ABSTRACT

Direct esterification of a labile alkoxyamine $R^1R^2NOR^3$, which was previously reported as unsuccessful, is achieved by a Mitsunobu reaction or a nucleophilic substitution. Ester derivatives are obtained under smooth conditions and easily purified. Macrocyclization attempts on ester derivatives were successful for five-membered ring lactones and unsuccessful for 13-membered ring lactones. Moreover, the success of the cyclization was dramatically dependent on the quality of the solution degassing. Poor degassing led to unexpected carbonate alkoxyamine.

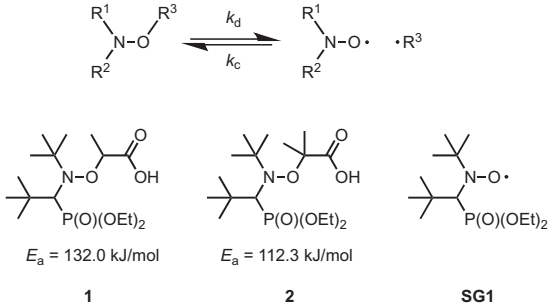
Alkoxyamines $R^1R^2NOR^3$ are labile molecules that can undergo homolysis of the C–ON bond under moderate heating to release nitroxides $R^1R^2NO\cdot$ and alkyl radicals $R^{3}\cdot$ Scheme 1). They are widely used in Nitroxide Mediated Polymerization (NMP) as initiator/controller agents,[1,2] and in Radical Organic Chemistry as a source of alkyl radicals.[3] It is therefore interesting to obtain complex alkoxyamines from functionalization of simple alkoxyamines: for example, synthesis of esters or amides from alkoxyamines bearing a carboxylic acid function.

Today, two of the most well known alkoxyamines are compounds **1** and **2**, based on the **SG1** nitroxide (Scheme 1). However, only limited functionalizations of alkoxyamines **1** and **2** have been reported (Scheme 2). Esterification of **1** has been already achieved,[4,5] but attempts to esterify **2** have failed, although it has successfully been converted into an amide such as **4**.[6]

Currently, if a specific ester derivative of alkoxyamine **2** is required, esterification has to be accomplished on the precursor of the alkyl part of **2** before its coupling with the nitroxide. To alleviate this difficulty, it would be desirable to have an efficient, direct way to functionalize the labile alkoxyamine **2**. Following our ongoing program of synthesis and physico-chemical evaluation of new alkoxyamines,[7,8] we report herein the investigation of the direct functionalization of the carboxylic moiety of alkoxyamine **2** into different esters.

Esterification reactions are generally achieved by activating a carboxylic function to a more electrophilic species that can undergo condensation with a nucleophilic alcohol. The most widely used method is the transformation of the carboxylic group into its corresponding acyl chloride by treatment with thionyl chloride. This method was successfully applied on alkoxyamine **1**, which carries only one methyl group in the α-position of the carboxylic group, affording the corresponding acyl chloride.[4,5,9] Similar attempts to make the acyl chloride of alkoxyamine **2** were not successful.[10] One should note that the carboxylic moiety of **2** is more hindered than that of **1**, as it contains an extra methyl group, and therefore the carboxylic group is in neopentylic position. Another approach relying on the use of DCC also failed.

During the last decade, relationship (1) was developed (at $T = 120\ ^\circ C$) to predict homolysis rate constant k_d from the electrical Hammett constant σ_I, the released radical stabilization constant σ_{RS}, and the steric effects of the alkyl fragment υ.[11] Then, assuming



Scheme 1. Homolysis of alkoxyamines and structures of labile alkoxyamines **1** and **2** (Ea: activation energy).

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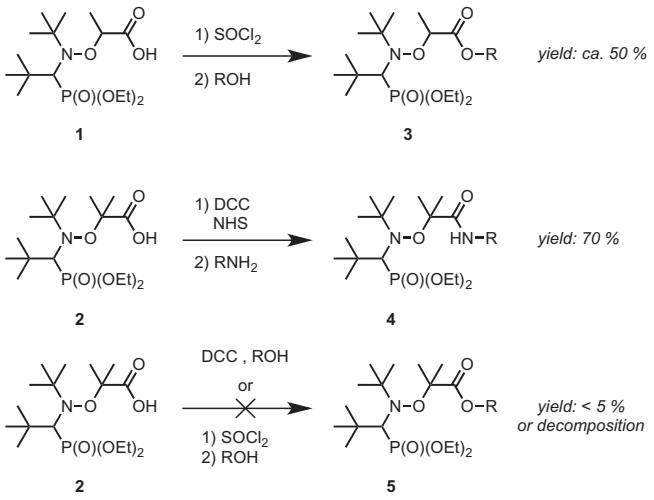
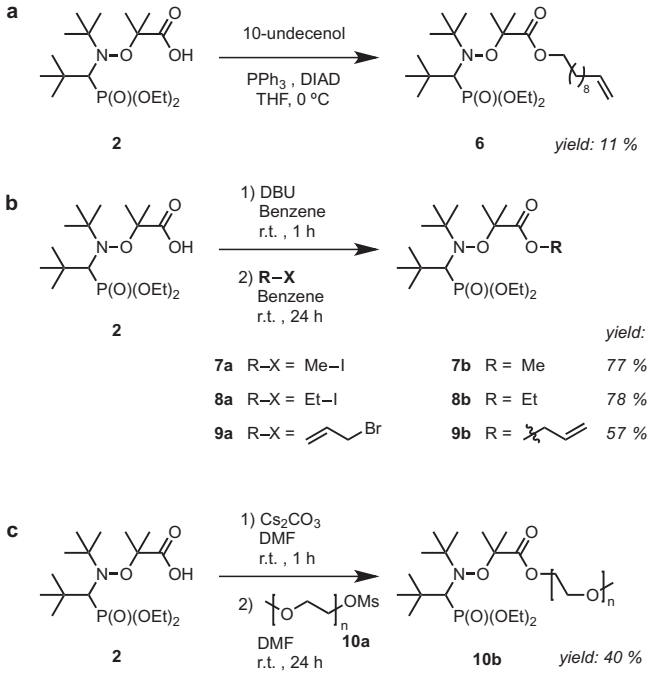


Scheme 2. Functionalization of alkoxyamines **1** and **2** by esterification and amidification, respectively.

that the effect of the acyl chloride COCl, the DCC-activated carboxylic group (CODCC) and the carboxylic group COOH functions are very similar on the stabilization of the released radical ($\sigma_{RS} = 0.21$)[11] and the bulkiness ($\upsilon = 1.24$)[11] of the alkyl fragment, the polar effect when going from carboxylic group ($\sigma_{COOH} = 0.36$)[12] to acyl chloride ($\sigma_{COCl} = 0.50$)[12] or DCC-activated[13] carboxylic group leads to a decrease in E_a of roughly 5 kJ/mol ($E_a = 107.0$ kJ/mol) to the COCl function, that is, a 4-fold increase in k_d at room temperature.[14] This increase in the dissociation constant in combination with a low reactivity of both the alcohol (poor nucleophile) and the carboxylic group in the neopentylic-like position favors the decomposition of intermediate acyl chloride[15] rather than the formation of the expected ester **5**.

$$\log(k_d/s^{-1}) = -14.3 + 15.3 \times \sigma_{RS} + 19.5 \times \sigma_I + 7.0 \times \upsilon \qquad (1)$$



Scheme 3. Direct esterification of alkoxyamine **2** by (a) Mitsunobu reaction, (b) nucleophilic substitution of alkyl halides, (c) application to polymer grafting.

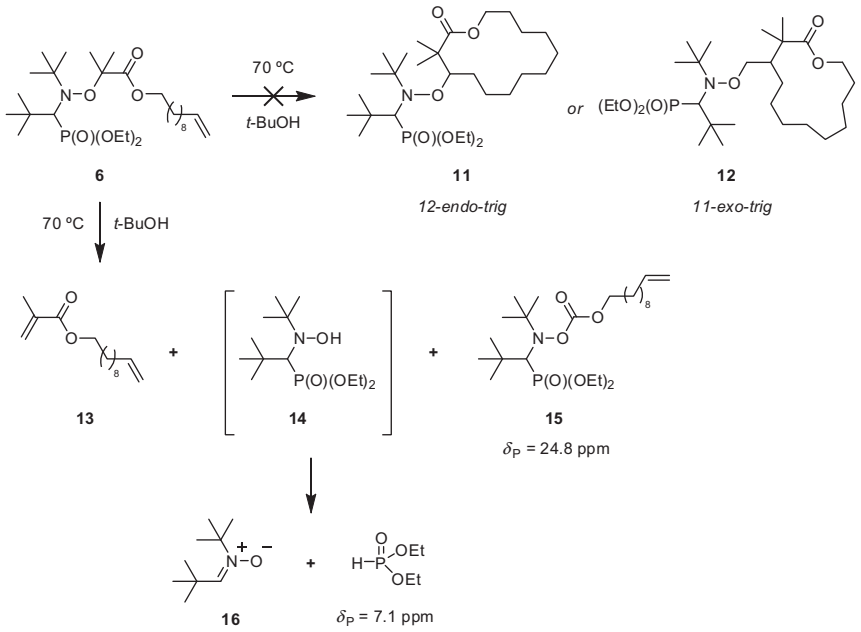
Recently, we showed a striking increase in k_d upon protonation or quaternization of the alkyl fragment, that is, increase in the electron withdrawing capacities of the alkyl fragment supporting the increase of k_d upon activation of the carboxylic group.[7,8] However, as *N*-hydroxysuccinimide (NHS) is a good nucleophile, it reacted fast enough with the DCC intermediate to afford the second-hand alkoxyamines suitable for reaction with amines and then affords amide **4** (Scheme 2).[6]

Analysis of relationship (1) in conjunction with the previous experimental results made it clear that esterification of **2** via activation of the carboxylic acid was likely to fail, with the possible exception of reaction with a highly nucleophilic alcohol. On the other hand, if the acid was deprotonated to form its carboxylate ($\sigma_{I,COO^-} = -0.13$), the C–ON bond homolysis would be deactivated,[16] and hence **2** might be derivatized into its ester under mild conditions. As a result, we changed our esterification strategy from activating the carboxylic acid moiety making the alcohol component to be the electrophilic species. First, we thought about the Mitsunobu reaction to save the pre-activation step of alcohol. After screening several conditions, the best result was obtained by adding alkoxyamine **2** and then 10-undecenol to a mixture of triphenylphosphine and diisopropylazodicarboxylate (DIAD) in THF. Obtaining the targeted ester **6** by direct functionalization of **2** was gratifying, despite a low 11% yield (Scheme 3a).[17] However, the Mitsunobu reaction is not suitable for large-scale reactions, due to the excess of reagents (Ph_3P, DIAD, acid and/or alcohol) and the byproducts obtained ($Ph_3P{=}O$, reduced DIAD), the latter requiring time-consuming and expensive purification techniques. It is also known that the Mitsunobu reaction can proceed through several different mechanistic pathways involving either activation of the alcohol, or activation of the acid.[18] These facts might explain partly why low yields were obtained.

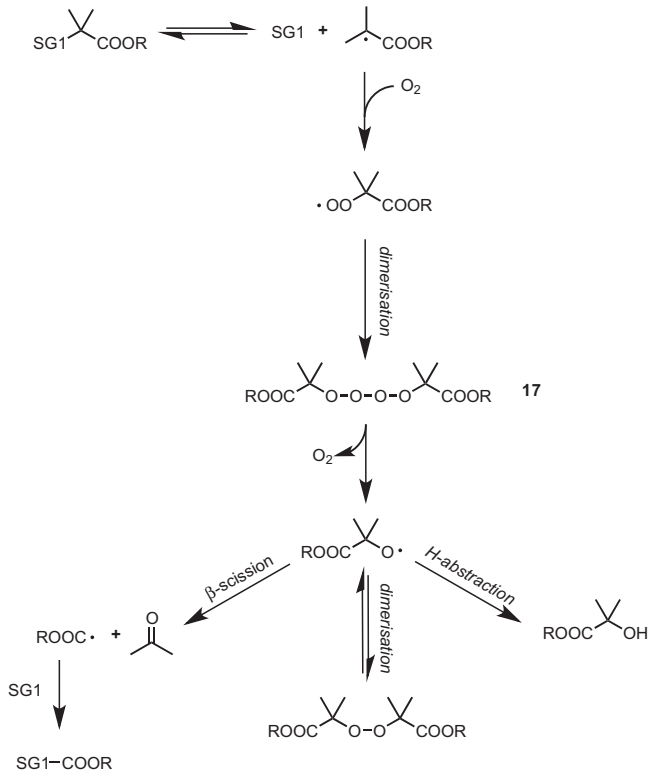
We then turned our attention to an even simpler method, using pre-activated alcohol such as halides or mesylates. After deprotonation of **2** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene, the resulting carboxylate was reacted with methyl iodide at room temperature for 24 h. The corresponding methyl ester **7b** was obtained in good yield (77%) after simple short filtration on silica gel, without work-up of the reaction.[19,20] The same conditions were successfully applied to ethyl iodide or allyl bromide and afforded ethyl ester **8b** in 78% yield[21] and allyl ester **9b** in 57% yield,[22] respectively. No traces of **SG1** were detected during these experiments, indicating that the homolysis of alkoxyamine species did not occur (Scheme 3b).

Compound **2** is one of the most efficient alkoxyamines for NMP.[1] Along its invaluable kinetic properties for NMP, the presence of a carboxylic group is very appealing for pre- or postpolymerization transformations. Such versatility has been nicely highlighted by the preparation of copolymers and armpolymers.[23] Thus, we decided to test our procedure of esterification by grafting a polyethylene glycol onto **2** to obtain **10b** (Scheme 3c). First, we tested the DBU/benzene procedure using monomethyl polyethyleneglycol mesylate **10a** as the electrophile, but no new products were observed by ^{31}P NMR. After screening several solvents (benzene, CH_2Cl_2, THF, DMF), smooth conditions using Cs_2CO_3 as the base and DMF as the solvent (24 h, room temperature) afforded the targeted grafted polymer **10b** in 40% conversion by ^{31}P NMR. Polymer was characterized by ^{31}P NMR and grafting was confirmed by ESI/MS.[24,25]

As exemplified with **1**, alkoxyamines carrying an alkenyl fragment are prone to undergo radical cyclization under thermal conditions ($T = 110$ °C).[4] A similar behavior for ester derivatives of alkoxyamine **2** was expected but at lower temperatures. Macrocyclization should occur by heating derivative **6** at 70 °C in *t*-BuOH[26] and should afford either *12-endo-trig* cyclic product **11** and/or *11-exo-trig* product **12**. Full conversion (48 h, $T = 70$ °C, degassing

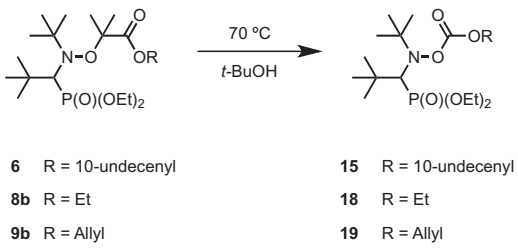


Scheme 4. Attempt of macrocyclization on alkoxyamine **6**.



Scheme 5. Proposed mechanism for the formation of the side-product SG1-COOR.

under moderate vacuum, $P = 10^{-2}$ Torr) was observed by ^{31}P NMR, and only two peaks were recorded at $\delta = 24.8$ ppm (80%) and $\delta = 7.1$ ppm (20%), the latter corresponding to diethyl phosphite $(EtO)_2P(O)H$. Indeed, H-atom abstraction from the alkyl radical by the nitroxide is well documented,[27] and in our case, it led to (undec-10-enyl)methacrylate **13** and hydroxylamine **14** (Scheme 4). The latter is reported to be thermally unstable and decomposes into nitrone **16** and diethylphosphite.[28,29] The presence of a signal

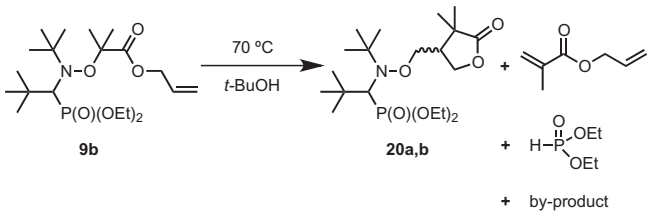


6 R = 10-undecenyl
8b R = Et
9b R = Allyl

15 R = 10-undecenyl
18 R = Et
19 R = Allyl

Scheme 6. Structure of compounds **15**, **18**, and **19**.

typical of alkene **13** was observed by ^{1}H NMR ($\delta = 6.10$ ppm) confirming the occurrence of the H-atom abstraction reaction. However, the presence of other vinylic protons discarded the presence of the expected cyclic compounds **11** and/or **12**. After purification of the compound corresponding to the peak at $\delta = 24.8$ ppm in ^{31}P NMR, ^{1}H NMR confirmed the presence of vinylic protons precluding the cyclic compounds **11** and/or **12** and showed the absence of two methyl groups. ESI–MS analysis showed a loss of 42 units of mass and ^{13}C NMR showed that indeed two methyl groups and a quaternary carbon were missing, when comparing with the starting materials. The same observations were made for **8b** and **9b** for samples prepared in the same way. Furthermore, when experiments were performed in deuterated benzene in an NMR probe, the typical signal of acetone was recorded. Consequently, it led us to assume that the reactivity observed can be rationalized invoking the conventional decomposition of the tetroxide **17** as intermediate (Scheme 5). That is, as the cross-coupling between nitroxide and tertiary alkyl radical was strongly disfavored, the alkyl radical reacted with oxygen to afford an alkyl peroxyl radical. As the latter had no other possibilities than to react by self-termination, it afforded a tetroxide species **17** that spontaneously decomposed into oxygen and alkoxyl radicals. As alkoxyl radicals cannot react with nitroxide and as no labile H-atoms were available, its β-fragmentation was favored to afford acetone and the stabilized acyl radical.[30,31] Then, the latter reacted by cross-coupling to afford by-products **15**, **18**, and **19** from **6**, **8b**, and **9b**, respectively (Scheme 6).[32–34]



Scheme 7. Cyclization of compound **9b**.

When experiments were performed on samples degassed under high vacuum (48 h, $T = 70$ °C, degassing under high vacuum, $P = 10^{-5}$ Torr) a totally reverted reactivity was observed, that is, 20% of side-products **15**, **18**, **19** and 80% of diethylphosphite, and new trace peaks were also observed for **9b** (*vide infra*).[35] It nicely confirmed the influence of oxygen on the reactivity and its role in the proposed mechanism. The kinetics and the consequence of this mechanism on the reactivity of labile alkoxyamines are currently under investigation.[29] For **9b** experiment was again performed in high vacuum-sealed tube and peaks at $\delta = 23.0$ and $\delta = 23.3$ ppm were observed by ^{31}P NMR along with **14** and diethylphosphite. It is likely that the formation of large rings (14 to 15 members) is strongly entropically disfavored and cannot compete with the H-atom abstraction leading to hydroxylamine and alkyl methacrylates involving that large rings cannot be prepared with this procedure. The formation of five-membered ring lactone was reported for alkoxyamine based on **1**.[4] The new peaks aforementioned are in the expected zone for this family of compounds. Thus, experiment was performed on a preparative scale by heating a *t*-BuOH solution of **9** degassed under high vacuum ($P = 10^{-5}$ Torr) in a sealed Schlenk at 120 °C for 2 h. Full conversion was reached by ^{31}P NMR, affording 66% of **20a** and **20b** (50% isolated yield) and 34% of diethylphosphite. The vinylic protons at $\delta = 5.89$ ppm confirmed the presence of allyl methacrylate **21** and hence the mechanism of its generation (Schemes 4 and 7). The ^{1}H, ^{31}P, and ^{13}C NMR confirmed the *5-exo-trig*-cyclization as no vinylic protons were detected, as new CH_2O ($\delta = 71.78$ ppm and $\delta = 67.80$ ppm for **20a** and $\delta = 72.13$ ppm and $\delta = 67.99$ ppm for **20b**) and CH ($\delta = 43.18$ ppm for **20a** and $\delta = 42.92$ ppm for **20b**) signals were arising.[36] Furthermore the HRMS confirmed the expected mass.[37]

In conclusion, we achieved direct esterification of the labile alkoxyamine **2** by two different methods: (1) a Mitsunobu reaction followed by tedious purification, (2) a very simple nucleophilic displacement of an alkyl halide by the carboxylate anion of **2** followed by simple filtration through silica gel. This last method allows several ester derivatives of the labile alkoxyamine **2** to be obtained directly and efficiently without pre-coupling functionalization. The preparation of the polymeric initiator **10b** in good yield highlights the potential of such type of functionalization for applications in Polymer Science.

We showed that the radical cyclization of large rings cannot be performed with alkoxyamines derived from **2**. On the other hand, formation of five-membered ring lactone was performed in moderate yield. In fact, with these examples, the limits of the Persistent Radical Effect are reached, as the cross-coupling reaction is so slow that it cannot compete with the H-atom abstraction side-reaction and cannot play its role of prolonging the lifetime of the alkoxyamine until it reacts through the targeted reaction.

We also showed that the presence of oxygen might be an important issue as it led to new by-products. This reaction took place only because the cross-coupling reaction between nitroxide and alkyl radical was extremely slow. The consequences of this kinetic behavior on Nitroxide Mediated Polymerization issue are currently under investigation and will be reported in due course.

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17. *Undec-10-en-1-yl 2-((tert-butyl(1-(diethoxyphosphoryl)-2,2-dimethyl-propyl)-amino)oxy)-2-methylpropanoate (**6**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.09 (9H, s), 1.19 (9H, s), 1.25–1.32 (18H, m), 1.59 (3H, s), 1.70 (3H, s), 3.27 (1H, d), 3.90–4.10 (4H, m), 4.32–4.38 (2H, m), 4.92–5.01 (2H, m), 5.77–5.83 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.18, 16.27, 16.57, 16.65, 25.95, 28.13, 28.24, 28.52, 28.86, 29.04, 29.18, 29.35, 29.42, 30.01, 30.08, 33.75, 35.93, 36.01, 61.74, 61.82, 62.17, 64.95, 69.19, 71.02, 83.84, 114.12, 139.10, 175.29 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.3 ppm. HRMS (ESI): *m/z* calcd for $C_{28}H_{57}N_1O_6P_1$ $(M+H)^+$ 534.3918, found 534.3917.
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21. *Ethyl 2-((tert-butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)amino)oxy)-2-methylpropanoate (**8b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s), 1.19 (9H, s), 1.26–1.32 (9H, m), 1.59 (3H, s), 1.70 (3H, s), 3.27 (1 H, d, $J = 26.0$ Hz), 3.91–4.03 (1H, m), 4.07–4.11 (1H, m), 4.12–4.19 (2H, m), 4.33–4.39 (2H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.08, 16.21, 16.30, 16.56, 16.64, 22.45, 28.13, 29.98, 30.05, 35.95, 36.04, 60.77, 61.77, 61.85, 62.17, 69.24, 71.05, 83.74, 175.26 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.3 ppm. HRMS (ESI): *m/z* calcd for $C_{19}H_{41}N_1O_6P_1$ $(M+H)^+$ 410.2666, found 410.2673.
22. *Allyl 2-((tert-butyl(1-(diethoxyphosphoryl)-2,2-dimethylpropyl)amino)oxy)-2-methylpropanoate (**9b**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (9H, s), 1.19 (9H, s),

1.28 (3H, t, J = 7.0 Hz), 1.29 (3H, t, J = 7 Hz), 1.62 (3H, s), 1.71 (3H, s), 3.27 (1H, d, J = 26.0 Hz), 3.91–3.97 (1H, m), 4.03–4.09 (1H, m), 4.30–4.37 (2H, m), 4.59 (2H, d, J = 6 Hz), 5.23–5.34 (2H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.21, 16.30, 16.56, 16.64, 22.62, 27.99, 29.99, 30.06, 35.96, 36.04, 61.86, 61.94, 62.24, 65.53, 69.25, 71.06, 83.77, 118.68, 132.11, 174.81 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 25.3 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{41}N_1O_6P_1$ $(M+H)^+$ 422.2666, found 422.2669.

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32. *Diethyl (1-(tert-butyl(((undec-10-en-1-yloxy)carbonyl)oxy)amino)-2,2-dimethyl propyl)phosphonate (**15**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.20 (9H, s), 1.26–1.36 (18H, m), 1.57–1.68 (2H, m), 2.0–2.07 (2H, m), 3.26 (1H, d, J = 24.0 Hz), 4.05–4.30 (6H, m), 4.91–5.01 (2H, m), 5.74–5.88 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.28, 16.37, 16.50, 16.57, 27.59, 28.33, 28.40, 28.67, 28.90, 29.07, 29.35, 29.41, 33.87, 58.59, 58.88, 61.74, 61.82, 62.17, 64.95, 69.19, 71.02, 114.10, 139.18, 156.06 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.8 ppm. HRMS (ESI): m/z calcd for $C_{25}H_{51}N_1O_6P_1$ $(M+H)^+$ 492.3449, found 492.3442.
33. *Diethyl (1-(tert-butyl((ethoxycarbonyl)oxy)amino)-2,2-dimethylpropyl)phosphonate (**18**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (9H, s), 1.20 (9H, s), 1.26–1.34 (9H, m), 3.26 (1H, d, J = 24.0 Hz), 4.06–4.27 (6H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.29, 16.28, 16.34, 16.50, 16.56, 27.57, 28.34, 28.40, 36.13, 36.20, 60.14, 61.87, 62.72, 64.20, 67.82, 69.14, 155.94 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.7 ppm. HRMS (ESI): m/z calcd for $C_{16}H_{35}N_1O_6P_1$ $(M+H)^+$ 368.2197, found 368.2198.
34. *Diethyl (1-((((allyloxy)carbonyl)oxy)(tert-butyl)amino)-2,2-dimethyl-propyl) phosphonate (**19**).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (9H, s), 1.15 (9H, s), 1.25–1.28 (6H, m), 3.22 (1H, d, J = 24.0 Hz), 3.90–4.05 (4H, m), 5.09–5.27 (2H, m), 5.92–6.03 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.21, 16.29, 16.52, 16.59, 27.67, 29.69, 29.76, 35.54, 35.42, 58.86, 58.97, 61.74, 77.22, 78.26, 117.58, 134.03 ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ 24.5 ppm. HRMS (ESI): m/z calcd for $C_{17}H_{34}N_1O_6P_1$ $(M+H)^+$ 380.2197, found 380.2195.
35. Some oxidation products were still observed because the vacuum cap-closed tube is expected to be less tight all along the experimental period than the vacuum-sealed glass tube and leaks might occur.
36. The formation of six-membered ring (*6-endo-trig*-cyclization) is forbidden by the Baldwin's rules, and consequently such cyclization is not fast enough to compete with the side-reaction aforementioned.
37. *Diethyl (1-(tert-butyl((4,4-dimethyl-5-oxotetrahydrofuran-3-yl) methoxy)amino)-2,2-dimethylpropyl)phosphonate (**20a,b** 1:1 mixture of diastereomers).* ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.08 (3H, s), 1.10 (3H, s), 1.13 (9H, s), 1.14 (9H, s), 1.15 (9H, s), 1.16 (9H, s), 1.26–1.33 (14H, m), 3.23 (1H, d, J = 24.9 Hz), 3.25 (1H, d, J = 25.1 Hz), 3.89–4.19 (14H, m), 4.40 (1H, dd, J = 7.2; 9.0 Hz), 4.47 (1H, dd, J = 7.6; 9.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.60, 14.83, 16.85, 17.40, 21.77, 22.28, 24.47. 25.81, 25.90, 26.07, 26.60, 26.68, 27.92. 28.42, 28.65, 33.51, 38.80, 40.76, 42.92, 43.18, 57.83, 59.21, 60.10, 60.16, 66.03, 67.06, 67.24, 67.80, 71.78, 72.13, 177.74, 180.07 ppm. ^{31}P NMR (121 MHz, C_6D_6): δ 23.0, 23.2 ppm. HRMS (ESI): m/z calcd for $C_{20}H_{40}N_1O_6P_1$ $(M+H)^+$ 422.2666, found 422.2666.