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Functionalized Phosphonated Half-Cage Molecules as Ligands for Metal Complexes

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Phosphonated molecules, featuring a half-cage structure and a *N*-lateral chain with additional metal coordinating groups were designed as ligands of metal cations. These compounds were synthesized by a Diels–Alder (DA) strategy, using 1-diethoxyphosphoryl-1,3-butadiene and a series of *N*-substituted maleimides as dienophiles. Two cycloadducts, bearing a terminal primary alcohol and a terminal iodide, respectively, were used as key intermediates for further functionalizations. Metal coordination properties of the ligands equipped with functionalized *N*-lateral chains were proven by an ESI-HRMS study. The stoichiometry of one selected Eu^{III} complex with a diphosphonated ligand was determined by photoluminescence spectroscopy in emission mode.

Introduction

Phosphonated molecules are used for various applications such as synthetic intermediates in organic chemistry and drug designs,[1] hybrid materials,[2] grafting functions on metallic surfaces,[3] and construction of supramolecular self-assemblies,[4] among others. In most cases, these systems take advantage of the metal coordination properties of the phosphonate group. Contrary to phosphonic acids,[5] in the literature, dialkyl phosphonates (i.e., esters) are rarely used as coordinating groups, although their coordination ability for divalent or trivalent metal cations was demonstrated in the case of simple molecules, namely diethyl (benzoyl)phosphonate,[6] diethyl (phthalimidomethyl)phosphonate,[6] and tetraethyl methylenediphosphonate.[7]

Previously, we disclosed a new family of phosphonated ligands featuring a half-cage structure. They were prepared by a [4+2] cycloaddition of 1-diethoxyphosphoryl-1,3-butadiene to cyclic C=C and N=N dienophiles.[8] The aim of this paper is to further document the syntheses of such ligands, equipped with a flexible linker terminated by an additional metal coordinating group. For that purpose, the scope of the Diels–Alder (DA) reactions of 1-diethoxyphosphoryl-1,3-butadiene with *N*-substituted maleimides has been enlarged thanks to the syntheses of new maleimide derivatives, on the one hand, and the postfunctionalization of selected cycloadducts, on the other hand. The presence of sensitive functional groups on both reagents and products makes this chemistry quite difficult, with arduous purifications of the final targets. The complexing properties of the new compounds toward di- and trivalent metal cations in solution have been assayed using high resolution mass spectrometry (HRMS) with electrospray ionization (ESI) and photoluminescence spectroscopy as the analytical tools.

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Results and Discussion

1. Synthesis of New Phosphonated Ligands

1.1 General Strategy

Our strategy relies on a Diels–Alder reaction between 1-diethoxyphosphoryl-1,3-butadiene and *N*-functionalized maleimides to give the phosphonated bicyclic frameworks with a half-cage shape resulting from the *all-cis* stereochemistry imposed by the [4+2] cycloaddition mechanism (see Figure 1).[8] The nitrogen atom of the imide function appears as the obvious anchoring point of the ω-functionalized linker designed to enhance the coordination properties of the molecule (see Figure 1, structure **I**). The introduction of the additional functional groups (FG) could be envisaged either before or after the [4+2] cycloaddition step, depending on the availability of the maleimide dienophiles. The dimer-like bis(phosphonated) molecules are also considered in this work (see Figure 1, structure **II**).

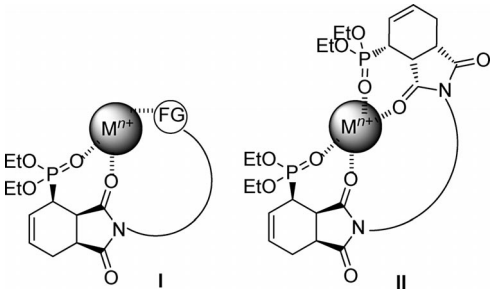
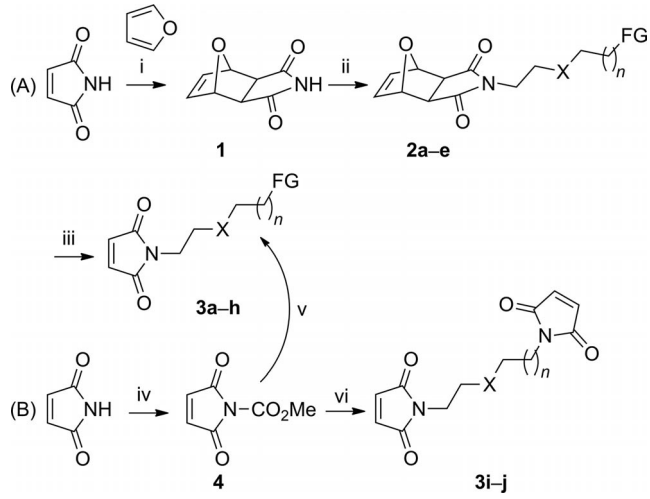


Figure 1. Design of phosphonated bicyclic ligands for metallic ion coordination.

The choice of the *N*-functionalized linkers depends on different parameters, such as the length and nature of the chain and the type of terminal group. A linker with five to six bonds should be long enough to allow for the contribution of the FG to the complexing pocket formed by the P=O and C=O functions of the bicyclic framework. We have considered alkyl and alkoxyalkyl chains as well as a variety of ancillary metal coordinating groups, such as the nitrile, amine, hydroxy, carboxylate, carbonyl, pyridyl, phosphonate, phosphate, and triazolyl functional groups.

Several strategies for the preparation of *N*-substituted maleimides are described in the literature. The classical method for preparing *N*-alkylated maleimide derivatives consists of a condensation reaction between primary amines and maleic anhydride followed by an acid-promoted intramolecular dehydration.[9] Using this method, maleimides are obtained in modest yields because of the poor efficacy of the second step. An alternative method uses *N*-(methoxycarbonyl)maleimide, under mildly basic conditions, in the direct condensation with commercially available amines.[10] The old method of Lerner and Schwartz,[11] based on the substitution of alkyl bromides by the silver or mercury salt of maleimide, offers a limited scope. The Mitsonobu reaction between maleimide and aliphatic alcohols gives access to *N*-substituted maleimides, but the removal of the byproducts could be sometimes difficult.[12] In Turnbull's procedure, the C=C double bond of maleimide is previously protected from a Michael addition by a Diels–Alder reaction with furan.[13] The furan–maleimide cycloadduct is then alkylated with alkyl bromides in the presence of potassium carbonate in DMF (*N*,*N*-dimethylformamide). Finally, the C=C double bond is deprotected by simple heating, and the retro Diels–Alder reaction releases the volatile furan.[14] This sequence of reactions is widely applied in polymers and materials science.[14]

For our purpose towards the preparations of *N*-substituted maleimides, two methods have been selected: (1) the alkylation reaction of the furan–maleimide cycloadduct (Method A) and (2) the substitution reaction of *N*-(methoxycarbonyl)maleimide with amines (Method B). These routes appear complementary for the preparation of various derivatives with a lateral chain bearing different terminal groups (see Scheme 1).



Scheme 1. Synthesis of *N*-substituted maleimides (Methods A and B). Reagents and conditions: (i) toluene, 110 °C, 48 h; (ii) $Br(CH_2)_2XCH_2(CH_2)_nFG$, K_2CO_3, DMF, 50 °C; (iii) DMF, 180 °C; (iv) $ClCO_2Me$, NMM (*N*-methylmorpholine), EtOAc, 0 °C; (v) $NH_2(CH_2)_2XCH_2(CH_2)_nFG$, $NaHCO_3$, H_2O, 0 °C to room temp.; (vi) $NH_2(CH_2)_2XCH_2(CH_2)_nNH_2$, $NaHCO_3$, H_2O, 0 °C to room temp.; see Table 1 for yields.

1.2 Synthesis of Maleimides

Maleimides **3b**–**3e** were prepared using Method A, because of the presence of sensitive terminal functional groups (see Scheme 1 and Table 1, Entries 2–5). Furan–maleimide cycloadduct **1** was obtained as a mixture of *endo* and *exo* diastereoisomers, but under prolonged heating, only the *exo* diastereoisomer (thermodynamic product) was present.[15] The alkylation step was first tested with 1-bromohexane in DMF at 50 °C, in the presence of potassium carbonate. Mixtures of the *endo* and *exo* isomers of **1** in various ratios were used, giving variable yields of **2a** (FG = Me) as mixtures of *endo* and *exo* isomers. The *exo* isomer **1** appeared more reactive. Moreover, the retro Diels–Alder decomposition of **2a** into **3a** occurred at a lower temperature for the *exo* isomer than for the *endo* isomer. Therefore, cycloadduct **1** containing a high content of the *exo* isomer was employed for the synthesis of **2b**–**2e** (see Scheme 1). These maleimide precursors were purified by column

Table 1. Yields of maleimides **3** and cycloadducts **5**.

Entry	X	*n*	FG	**3** (% yield[a], method)	**5** (% yield)
1	CH_2	1	Me	**3a** (20–60, A)[13]	**5a** (48)
2	CH_2	2	Cl	**3b** (59, A)	**5b** (58)
3	CH_2	2	CN	**3c** (51, A)	**5c** (48)
4	CH_2	2	NHBoc	**3d** (33, A)	**5d** (68)
5	CH_2	0	CCH	**3e** (32, A)	**5e** (46)
6	CH_2	1	OH	**3f** (53, B)[10a]	**5f** (58)
7	CH_2	2	OH	**3g** (55, B)[10a]	**5g** (56)
8	O	1	OH	**3h** (44, B)[10b]	**5h** (28)
9	CH_2	2	Mal[b]	**3i** (55, B)[16]	**5i** (16)
10	O	1	Mal[b]	**3j** (50, B)	**5j** (17)

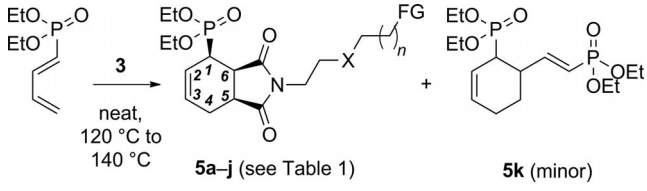
[a] For Method A, the yields are calculated from furan–maleimide cycloadduct (over 2 steps). For Method B, the yields are calculated from *N*-(methoxylcarbonyl)maleimide (in 1 step). [b] Maleimide functional group.

chromatography and directly deprotected by a retro Diels–Alder reaction in DMF at 180 °C to yield maleimides **3b**–**3e** without any purification (see Table 1). The overall yields of maleimides **3a**–**3e** diminished, when DMF was replaced by acetonitrile in the synthetic process.

Maleimides **3f**–**3j** were easily synthesized using Method B (see Scheme 1) by the reaction of **4** with amino alcohols to give **3f**–**3h** (see Table 1, Entries 6–8)[10a,10b] and with diamines to yield bis(maleimides) **3i**–**3j** (see Table 1, Entries 9 and 10).[16]

1.3 Cycloaddition of 1-Diethoxyphosphoryl-1,3-butadiene

Depending on the method for the preparation of maleimides **3**, two sets of reaction conditions were selected. Using Method A, maleimides **3a**–**3e** were obtained in a concentrated solution of DMF. Therefore, cycloadducts **5a**–**5e** were formed by a reaction of **3a**–**3e** with 1-diethoxyphosphoryl-1,3-butadiene[17] in a small volume of DMF at 120 °C (see Scheme 2 and Table 1, Entries 1–5). Using Method B, the DA reactions between 1-diethoxyphosphoryl-1,3-butadiene and maleimides **3f**–**3j** were conducted under solvent-free heating, and microwave activation did not improve the yields (see Scheme 2 and Table 1, Entries 6–10). The reaction temperatures were fixed at 120 and 140 °C for the syntheses of monophosphonated (**5f**–**5h**) and bis(phosphonated) cycloadducts (**5i**–**5j**), respectively.



Scheme 2. DA cycloaddition of 1-diethoxyphosphoryl-1,3-butadiene.

Purification of the cycloadducts **5a**–**5j** by column chromatography was necessary for the separation of byproduct **5k**, arising from the dimerization of the diene.[18]

Table 2. Typical coupling constants of cycloadducts **5** and related dihedral angles.

Atoms	^3J range (Hz)	Mean value (Hz)	Dihedral angle (°)
H-6, P	16.3–20.4	18.9	H-6–C-6–C-1–P (131)
H-1, H-6	4.7–7.0	5.8	H-1–C-1–C-6–H-6 (35)
H-5, H-6	9.1–9.5	9.3	H-5–C-5–C-6–H-6 (30)

The moderate to low yields of the final products were due to several purifications (see Table 1).

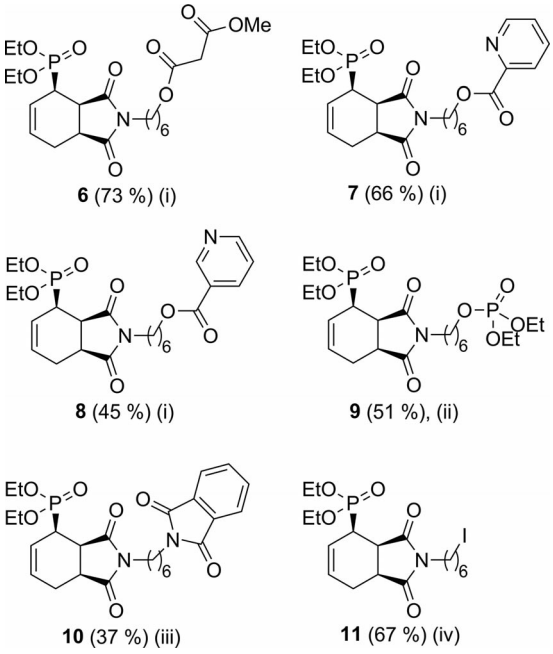
Cycloadducts **5a**–**5j** were characterized by ^{1}H, ^{13}C, and ^{31}P NMR spectroscopy. The coupling constants $^3J_{H,H}$ and $^3J_{H,P}$ were measured from the ^{1}H NMR spectra (see Table 2), and the related dihedral angles were deduced from the Karplus rule. As expected,[8a] the *all-cis* relative stereochemistry was confirmed.

1.4 Postfunctionalization of Selected Cycloadducts

Attemps to substitute the chlorine atom of **5b** with a phosphonated group through the Michaelis–Becker reaction failed (degradation). Conditions for *N*-Boc (*tert*-butoxycarbonyl) deprotection led to the degradation of **5d**, and conditions for the hydrolysis or reduction of the nitrile function were not compatible with the stability of **5c**. Surprisingly, we were unable to perform CuAAC [copper(I)-catalyzed alkyne–azide cycloaddition] reactions starting from acetylene derivative **5e**.

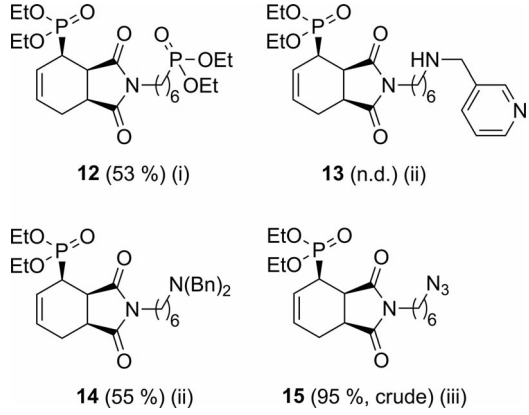
Cycloadduct **5g**, with a terminal alcohol functional group, was thus selected for the postfunctionalization experiments as the first key intermediate. Through O-acylation of **5g** with acid chlorides in the presence of triethylamine as a base in refluxing dichloromethane, acetylacetonate **6** and pyridine compounds **7** and **8** were produced (see Scheme 3). After purification on column chromatography, products **6**, **7**, and **8** were obtained in moderate to good yields. Under the same experimental conditions, treatment with chloroformates led to O-acylation directly followed by nucleophilic substitution by the chloride anion to give **5g**, which was previously prepared by Method A. A phosphate group was introduced by phosphorylation of the terminal alcohol of **5g** with diethyl chlorophosphonate and triethylamine in refluxing dichloromethane (DCM). After purification by column chromatography, **9** was recovered in moderate yield (see Scheme 3). Through a Mitsonobu reaction, the alcohol of **5g** was replaced with a phthalimide group (see Scheme 3). Because of the high polarity of product **10**, the use of triphenylphosphane supported (Ph_3P–PS) on a polymer was necessary for simplifying the purification, as the triphenylphosphane oxide (byproduct) could not be separated by column chromatography. Lastly, **5g** was transformed into iodide **11** through the Appel reaction to obtain a second key intermediate (see Scheme 3). Here again, the supported triphenylphosphane was required as the reagent. After purification by column chromatography, product **11** was obtained in good yields.

The Michaelis–Becker reaction, which failed with the chloride precursor **5b**, was successfully performed starting from the corresponding iodide **11**. Accordingly, a second phosphonate group was introduced by iodide substitution, yielding diphosphonated product **12** (see Scheme 4). The substitution of a phosphonate group by both primary and secondary amines was also possible (see Scheme 4). An excess amount of picolamine was necessary for a complete conversion into **13**, but unfortunately, the picolamine could



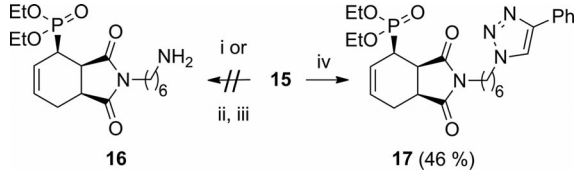
Scheme 3. Derivatives obtained from alcohol **5g**. Reagents and conditions: (i) acid chloride, Et_3N, DCM, reflux; (ii) $ClPO(OEt)_2$, Et_3N, DCM, reflux; (iii) phthalimide, DEAD (diethyl azodicarboxylate), Ph_3P–PS, THF (tetrahydrofuran), –78 °C to reflux; (iv) I_2, Ph_3P–PS, imidazole, THF, room temp.

not be totally eliminated either by solvent–solvent extraction or by column chromatography. With 1 equiv. of dibenzylamine, the complete conversion into **14** was observed, but the product was isolated in only moderate yields after purification. The reaction of **11** with tetrabutylammonium azide in refluxing acetonitrile furnished **15** quantitatively (see Scheme 4), and the advancement of this substitution reaction was followed by using FTIR spectroscopy (C–N_3 bond). Product **15**, protected from the light, was not purified, because of the instability of azide function on silica gel.



Scheme 4. Derivatives obtained from iodide **11**. Reagents and conditions: (i) $NaPO(OEt)_2$, THF, room temp.; (ii) amine, NEt_3, ACN (acetonitrile), reflux, n.d.: not determined; (iii) $N_3N(nBu)_4$, ACN, reflux.

The free amine **16** (FG = NH_2) was desirable as a starting material for further elaboration to the triazole and tetrazole motifs. Deprotection of the phthalimido group (FG = FtN) of **10** could not be performed under conditions that were compatible with the stability of the phosphonate ester and selective for the phthalimido group versus the imide function fused to the six-membered ring. The dibenzyl motif of **14** (FG = NBn_2) could not be properly deprotected, and all attempts to reduce **15** (FG = N_3) failed. A catalytic hydrogenation, a hydrogen transfer, and Staudinger reactions were tested without success (see Scheme 5), with only recovery of the degradation products. Interestingly, the crude azide **15** could be engaged in a CuAAC reaction to furnish triazole **17** with a maximum conversion of 74% and an isolated yield to 46% after column chromatography.



Scheme 5. Derivatives obtained from azide **15**. Reagents and conditions: (i) Ph_3P–PS, THF, room temp., H_2O/THF, reflux; (ii) H_2, Pd/C, AcOH, EtOH, room temp.; (iii) HCO_2NH_4, Pd/C, EtOH, reflux; (iv) phenylacetylene, $CuSO_4{\cdot}5H_2O$, sodium ascorbate, *t*BuOH/H_2O, room temp.

2. Metal Coordination Study

2.1 ESI-HRMS Analysis

Representative ligands (L) were considered for coordination with di- and trivalent metal (M) cations in ethanol and acetonitrile. Solutions of ligand (0.5 mM) were treated with 5 equiv. of anhydrous $M^{II}(ClO_4)_2$ or $M^{III}(NO_3)_3$ salts, and the mixtures were analyzed by HRMS in the electrospray (ESI) mode, a mild method allowing the transfer of the complexes in the gas phase with the conservation of non-covalent bonds (see Experimental section).[19] All of the complexes identified by ESI-HRMS were monocharged and possessed one or two poorly coordinating counteranion(s), that is, one perchlorate anion in the case of a divalent metal and two nitrate anions in the case of a trivalent metal. The results were confirmed by fragmentation experiments in the mass source, as perchloric acid or nitric acid fragments were lost (see Experimental Section and Supporting Information, Tables S1 and S2).

The main complexes formed with cycloadducts **5f**, **5g**, and **5h** (see Scheme 2 and Table 1) with an alcohol group as the ancillary function (FG = OH) on the lateral chains were [1L:1M] and [2L:1M] complexes. The results collected in Table 3 give the relative percentages of [1L:1M] and [2L:1M] complexes formed in EtOH and ACN, considering the most abundant complex (for each experiment) as 100%. The corresponding atomic compositions and exact masses are given in the Supporting Information, and the structures are confirmed by the isotopic masses. Zn^{2+}, Eu^{3+}, and La^{3+} formed almost exclusively [1L:1M] complexes with the three

ligands **5f**, **5g**, and **5h** in acetonitrile, a solvent able to complete the coordination sphere of the metals. In ethanol, high amounts of [2L:1M] complexes appeared in the case of La^{3+}, featuring the larger ionic radius of the studied series of cations. The effects of the length of the spacers (**5f** and **5h** with five atoms; **5g** with six atoms) and the nature of the spacers (**5f** and **5g** with an alkyl chain; **5h** including an ether function) were not significant. It is noteworthy that contamination of the ligands **5f**, **5g**, and **5h** with the diene dimer (i.e., **5k**, see Scheme 2) was clearly visible in this HRMS study. Although not detected in the ^{1}H and ^{31}P NMR spectra, **5k** in trace amounts (<1%) formed [1L:1M] complexes with Zn^{2+} (see Table 3, Entries 1, 4, and 7). In one case (see Table 3, Entry 9), a [1L:1M] complex with Na^{+} was observed with the crown ether-like ligand **5h** (Na^{+} is a typical contaminant in ESI).

Table 3. Relative abundance of [1L:1M] and [2L:1M] complexes in ethanol and acetonitrile for the cycloadducts **5f**–**5h**.

Entry	Ligand[a]	Metal[b]	Relative % of complexes			
			EtOH		ACN	
			[1L:1M]	[2L:1M]	[1L:1M]	[2L:1M]
1[c]	**5f**	Zn^{2+}	100	3	100	6
2	**5f**	Eu^{3+}	100	0	100	1
3	**5f**	La^{3+}	93	100	100	18
4[c]	**5g**	Zn^{2+}	100	3	100	5
5	**5g**	Eu^{3+}	100	0	100	0
6	**5g**	La^{3+}	77	100	100	5
7[c]	**5h**	Zn^{2+}	100	0	100	0
8	**5h**	Eu^{3+}	100	0	100	0
9[d]	**5h**	La^{3+}	100	44	100	0

[a] Structures of ligand (L) given in Scheme 2 and Table 1. [b] $M^{2+}(ClO_4)_2$ and $M^{3+}(NO_3)_3$ salts. [c] Contamination with $[(\mathbf{5k}{\cdot}Zn)(ClO_4)]^{+}$. [d] Contamination with $[\mathbf{5h}{\cdot}Na]^{+}$.

Next, the behavior of the molecules equipped with the acetoacetyl- (i.e., **6**), pyridyl- (i.e., **7**) and triazolyl- (i.e, **17**) terminal groups and molecules with two P-containing functional groups (i.e., **5i**, **5j**, **9**, and **12**) was studied with a series of divalent (Ca^{2+}, Zn^{2+}, Mn^{2+}, and Mg^{2+}) and trivalent cations (Eu^{3+}, Sm^{3+}, La^{3+}, and Gd^{3+}) in ethanol solutions. In all cases, [1L:1M] complexes were identified by ESI-HRMS, without the occurrence of [2L:1M] complexes or complexes resulting from the presence of the contaminant **5k**. These results are consistent with the better coordination ability of ligands **5i**, **5j**, **6**, **7**, **9**, **12**, and **17** comparatively to **5f**–**5h**.

Lastly, the competition experiments were performed by considering either two ligands versus one metallic cation or two metallic cations versus one given ligand. For the competition tests between two ligands, the selectivity (see Table 4) was calculated from the ratio of the complexes formed from each ligand (area under the mass peaks, considering all types of complexes, [1L:1M], [1L:1M:EtOH], and [2L:1M]). Considering the reference ligand **5g** (FG = OH), the introduction of the additional phosphate function in **9** and the triazole motif in **17** increased the complexing ability of the phosphonated half-cage framework (see Table 4, Columns 1 and 2), particularly versus the Zn^{2+} and Gd^{3+} cations. The competition between the phosphate (i.e., **9**) and pyridyl (i.e., **7**) ligands was in favor of the phosphorus moieties complexing with Zn^{2+} (see Table 4, Column 3). However, the efficacy of the phosphate (i.e., **9**) and phosphonate (i.e., **12**) functional groups appeared quite similar (see Table 4, Column 4). Lastly, pairs of ligands with two P-containing functions were compared. The dimeric molecule **5i** was about ten times less efficient than **12** versus Zn^{2+} complexation, and both dimers **5j** and **5i** (differing by the nature of the spacer) were almost equipotent (see Table 4, Columns 5 and 6). The behavior of the ligands with two P-containing functions (**12**, **5i**, and **5j**) versus Eu^{3+} was quite similar (see Table 4, Columns 5 and 6).

Table 4. Competition experiments demonstrating the selectivity of pairs of ligands versus one given cation.[a]

Cations	Columns and pairs of ligands					
	1	2	3	4	5	6
	9/5g	**17/5g**	**9/7**	**9/12**	**12/5i**	**5j/5i**
Zn^{2+}	4.26	1.83	9.21	1.66	9.33	1.24
Ca^{2+}	1.47	1.45	n.d.[b]	n.d.	n.d.	n.d.
Gd^{3+}	2.89	2.66	n.d.	n.d.	n.d.	n.d.
La^{3+}	1.10	1.35	1.08	1.16	n.d.	n.d.
Eu^{3+}	n.d.	n.d.	n.d.	n.d.	1.17	1.57

[a] 0.25 mM for each ligand vs one given cation (5 equiv.). [b] n.d.: not determined.

Competition experiments of one ligand (0.5 mM) versus two metals (2.5 equiv. for each metal) were also performed in ethanol. The reference cycloadducts **5f**–**5h** (FG = OH) appeared to be selective for Eu^{3+} over La^{3+} [selectivity of Eu^{3+}/La^{3+}, 15.5 (for **5f**), 17.5 (for **5g**), and 27.6 (for **5h**)]. In this experiment, the effect of the nature of the spacer was more visible, that is, **5h** that includes an ether function was two times more potent than **5f** with the corresponding alkyl spacer. The ligands functionalized by an additional phosphate group (i.e., **9**) and triazole groups (i.e., **17**) coordinated more with Zn^{2+} than with Mn^{2+} [selectivity of Zn^{2+}/Mn^{2+}, 6.50 (for **9**) and 8.75 (for **17**)] and with La^{3+} [selectivity of Zn^{2+}/La^{3+}, 8.91 (for **9**)]. Compounds **9** and **17** also coordinated more with Gd^{3+} [selectivity of Gd^{3+}/La^{3+}, 5.08 (for **9**) and 10.06 (for **17**)] and Sm^{3+} [selectivity of Sm^{3+}/La^{3+}, 9.16 (for **9**)] than with La^{3+}.

The HRMS study allowed us to obtain information about the nature of the formed complexes and the selectivity of the ligands towards different metal cations in the gas phase. This method did not give access to the real stoichiometry of the complexes, in solution or in solid state. Because the isolation of crystalline complexes was not possible, the stoichiometry was determined by titration in solution.

2.2 Photoluminescence

Diphosphonated ligand **12**, showing excellent metal coordination properties in the ESI-HRMS analysis, was selected for a more detailed study using a luminescent cation. This ligand itself was not fluorescent. The stoichiometry of the ligand **12**/Eu^{III} complex was determined by the differ-

ence in emission intensities between the "free" Eu^{III} cation, from the $Eu(NO_3)_3{\cdot}5H_2O$ solution, and the coordinated Eu^{III} cation in its complex with **12**. When the excitation was made with Eu^{III} (λ = 395 nm), a small difference of emission intensities was observed between the "free" Eu^{III} nitrate and the ligand **12**/Eu^{III} coordination complex, so titration was not possible using this excitation wavelength. When the excitation was made with ligand **12** (λ = 244 nm), the energy of ligand was partially transferred to the complex metallic core through an antenna effect, and the coordination complex between **12** and Eu^{III} became more photoluminescent than the "free" Eu^{III}. The concentration of ligand was held almost constant during the titration, and a concentrated solution of $Eu(NO_3)_3{\cdot}5H_2O$ in acetonitrile was added by aliquots to the solution of **12** in acetonitrile. After each addition, a photoluminescence spectrum in emission mode was acquired in the Eu^{III} zone wavelengths (500–700 nm), after excitation at 244 nm (see Figure 2). A titration curve was drawn by recording the photoluminescence intensity of the most intense Eu^{III} band, corresponding to the $^5D_0 \rightarrow {}^7F_2$ transition,[20] as a function of the [Eu^{III}]/[ligand **12**] concentration ratio (see Figure 3). The curve presents two inflexion points (A and B), which correspond to the two different complexes formed in solution. The [2L:1M] complex is observed for a low Eu^{III} concentration (A), whereas the [2L:3M] ligand **12**/Eu^{III} complex is formed at a high Eu^{III} concentration (B). The complexes were recovered as viscous oils, and crystallization was impossible, so the exact structures, deduced from X-ray diffraction analysis of the monocrystals, are not accessible.

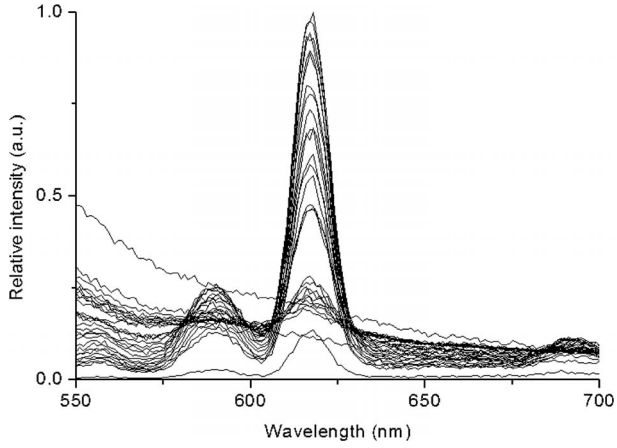


Figure 2. Photoluminescence spectra (emission mode, excitation at 244 nm) for the titration of ligand **12** from the ligand **12**/Eu^{III} complex in acetonitrile solution. Initial concentration of **12** = 0.113 M, addition of $Eu(NO_3)_3{\cdot}5H_2O$ from 0.00 equiv. to 3.08 equiv. from aliquots of 0.05 equiv.

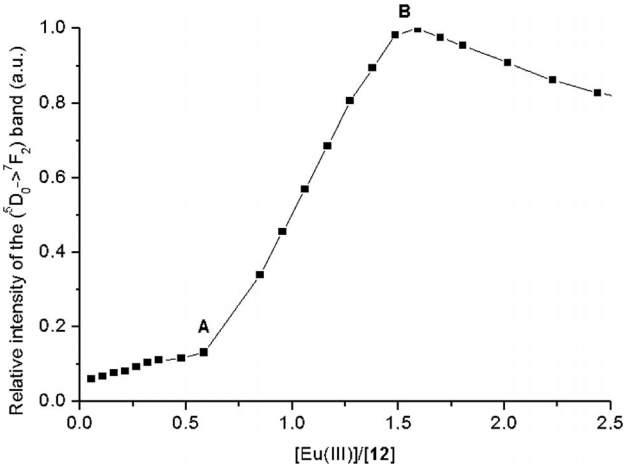


Figure 3. Titration curve for determining the stoichiometry of Eu^{III}/ligand **12** complex in acetonitrile solution.

At low Eu^{III} concentrations, two ligands coordinated to one metallic core. This stoichiometry is compatible with the coordination number of Eu^{III}, considering the involvement of two functional groups on the half-cage scaffold (phosphoryl and carbonyl groups) and two additional intramolecular coordinations by the terminal phosphonate group of the *N*-lateral chain. The coordination sphere of Eu^{III} is completed by the nitrate counterion and weakly coordinating molecules, such as water or acetonitrile. At high concentrations of Eu^{III}, two ligands coordinated with three metal cations. We hypothesize that each additional phosphonate group coordinates another Eu^{III} cation rather than one trapped by the half-cage structure (see Figure 4).

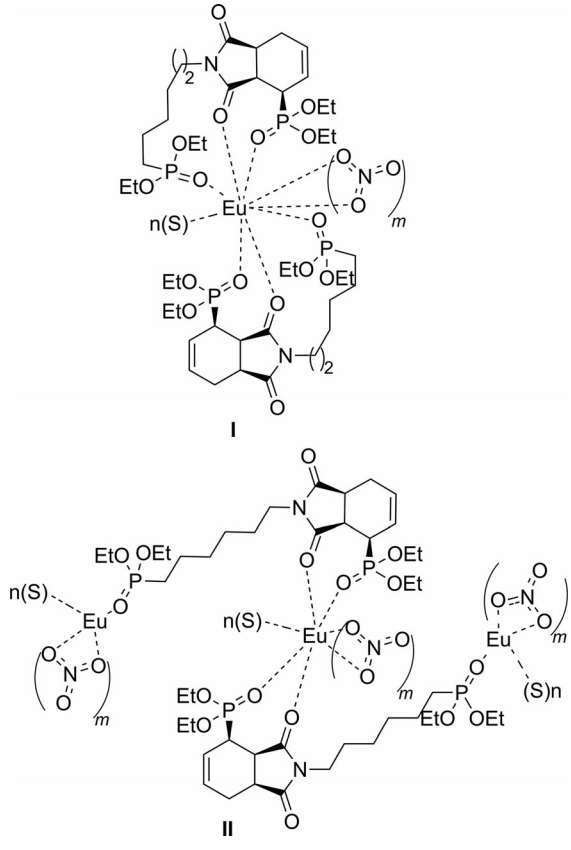


Figure 4. Possible structures of ligand **12**/Eu^{III} complexes in acetonitrile solutions. S = H_2O or ACN, m = 2, 3, 4, $n > 0$. Structure at low Eu^{III} concentration (**I**), structure at high Eu^{III} concentration (**II**).

Conclusions

We have successfully exploited the [4+2] cycloaddition of 1-diethoxyphosphoryl-1,3-butadiene and *N*-substituted maleimide derivatives to produce a small library of phosphonated bicyclic cycloadducts, particularly well adapted for coordination with metal cations, thanks to their butterfly shape that brings the P=O (from the diene) and C=O (from the dienophile) groups in spatial proximity to each other. A short arm (five to six atoms) terminated by different functional groups and attached to the imide nitrogen atom has been designed to achieve a good coordinating pocket. These ancillary groups were introduced before the DA reaction, that is, during the preparation of the dienophiles (FG = Cl, CN, NHBoc, CCH, OH, and Mal), or after the DA reaction by the postfunctionalization of two key cycloadducts, namely, **5g** (FG = OH) and **11** (FG = I), which is derived from **5g**. Using this latter strategy, the best coordinating groups could be inserted [FG = acac (acetylacetonate), pyridyl, $OPO(OEt)_2$, and $PO(OEt)_2$]. Unfortunately, all attempts to synthesize amine derivative **16** (FG = NH_2) from precursors **5d** (FG = NHBoc), **10** (FG = FtN), **14** (FG = NBn_2), and **15** (FG = N_3) failed. Therefore, the construction of azole motifs was not possible, with the exception of the phenyltriazole motif of **17** formed by a CuAAC reaction from **15** (FG = N_3) and phenylacetylene. It is noteworthy that the reverse CuAAC reaction of **5e** (FG = CCH) and phenylazide led to intractable mixtures. Besides the phosphonated bicyclic molecules equipped with a functionalized spacer arm (i.e., **6**–**9**, **12**, and **17**), two dimeric ligands (**5i** and **5j**) were obtained by the reaction of the phosphonodiene with bis(maleimides) **3i** and **3j**, respectively. All of the cited compounds have been purified (often with great difficulties because of the presence of the diene dimer **5k** and phosphonated degradation products) and characterized by NMR spectroscopy. The *all-cis* stereochemistry was confirmed by the H^6-P, H^1-H^6, and H^5-H^6 coupling constants.

The capacity for forming complexes with metal cations in solution was demonstrated by ESI-HRMS analyses. Exclusively, [1L:1M] complexes with Ca^{2+}, Zn^{2+}, Mn^{2+}, Mg^{2+}, Eu^{3+}, Sm^{3+}, La^{3+}, and Gd^{3+} were identified in the case of functionalized ligands **6**, **7**, **9**, **12**, and **17** and dimeric ligands **5i** and **5j**. Most probably, the P=O and C=O groups from the bicyclic core and the FG (or maleimide) are involved in the coordination sphere (see Figure 1). As a matter of fact, the reference compounds **5f**–**5h**, equipped with a poorly coordinating function (FG = OH), gave [1L:1M] and [2L:1M] complexes mainly with La^{3+}. The beneficial effect of the functionalized arm was further demonstrated through competition experiments versus **5g** (FG = OH). The best ancillary groups are the triazole, phosphate, and phosphonate groups, and this is particularly shown in the complexation with Zn^{2+}. The selectivity of particular ligands for one metal cation has been observed, but the results cannot be easily correlated with the ionic radii or in the framework of the HSAB (hard and soft, acids and bases) theory. Lastly, the photoluminescence properties of the complexes formed between Eu^{3+} and diphosphonated ligand **12** allowed for titration in solution, showing the evolution of the complex stoichiometry from [2L:1M] to [2L:3M] as the concentration of Eu^{3+} increases. The use of such complexes for the fabrication of hybrid materials endowed with light-responsive properties is under study.

Experimental Section

General Methods: All of the syntheses were performed under an argon atmosphere. The chemicals, purchased from Acros Organic, Alfa Aesar, and Sigma–Aldrich, were of reagent grade and used without purification. TLC analyses were performed on aluminium plates coated with silica gel (Merck 60 F-254), and flash column chromatography was performed over silica gel (230–400 mesh). Visualization of TLC plates was performed under a UV lamp (254 nm) and by using *p*-anisaldehyde or $KMnO_4$. Analytical grade solvents were used for the reactions, and the solvents for column chromatography were technical grade and distilled before use. Reactions under microwave heating were conducted in sealed tubes using MicroSYNTH equipment (Milestone Srl). The NMR spectroscopic data were recorded with a Bruker AVANCE II 300 spectrometer, operating at 300, 75, and 121 MHz for ^1H, ^{13}C, and ^{31}P NMR, respectively, and with a Bruker AVANCE II 500 spectrometer operating at 500, 125, and 202 MHz for ^1H, ^{13}C, and ^{31}P NMR, respectively. The chemical shifts are reported in ppm. Tetramethylsilane was used as the internal standard (δ = 0.0 ppm) for the ^1H NMR spectra. The internal standard was deuterated chloroform for the ^{13}C NMR spectra (δ = 77.16 ppm). ^{31}P NMR downfield shifts (δ) are expressed with a positive sign, using 85% H_3PO_4 in H_2O as the external standard. Spectroscopic data are reported in the order of chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet), coupling constant (Hz), integration, and assignment. The numbering of the atoms does not follow the IUPAC rules. The dienyl protons are referred to as H-1 to H-6, because this motif is common to all of the cycloadducts (see Table 2). Melting points were measured with a Büchi B-540 apparatus, calibrated with caffeine, vanillin, and phenacetin. Infrared spectra (IR) were recorded by transmittance with Schimadzu FTIR-8400S equipment, and the absorption bands are reported in cm^{-1}. The products are analyzed as thin films deposited on a Se-Zn crystal by evaporation from $CHCl_3$ solutions. The intensity of peaks is noted by (w), (m), and (s), respectively, for weak, medium, and strong. Mass spectra (MS) were recorded with a LCQ Finnigan MAT, and the masses are reported in Daltons. High Resolution Mass Spectrometry analyses (HRMS) were carried out at the University College London.

1. Syntheses

General Procedure for Cycloaddition to 1-Diethoxyphosphoryl-1,3-butadiene (Method A): A mixture of the diene (1 equiv.) and *N*-substituted maleimide **3a**–**3e** (1 equiv.) in dimethylformamide (**3**/DMF, from 80:20 to 90:10) was vigorously stirred at 120 °C for 4–12 h. The advancement of the reaction was controlled by ^{31}P NMR spectroscopy. The reaction mixture was directly purified by column chromatography on silica gel.

Diethyl 2-Hexyl-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5a): *N*-Hexylmaleimide (**3a**, 0.073 g, 0.403 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.077 g, 0.403 mmol) gave **5a** as a brown oil (70 mg, 48%). R_f = 0.4 (ethyl acetate). ^1H NMR (500 MHz, $CDCl_3$): δ = 6.09 [dtt, $^3J_{2,3}$ = 9.4, $^3J_{3,4}$ = $^4J_{1,3}$ = 4.7, $^4J_{3,P}$ = $^3J_{3,4'}$ = 1.7 Hz, 1 H, C(3)-H], 5.99 [dtt, $^3J_{2,3}$ = 8.5, $^3J_{2,P}$ =

$^3J_{1,2}$ = 5.9, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.5 Hz, 1 H, C(2)-H], 4.19 [q, ^3J = 7.1 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 4.09 [q, ^3J = 7.3 Hz, 2 H, PO(OCH_2-CH$_3$)$_2$], 3.46 (m, 2 H, NCH_2), 3.33 [ddd, $^3J_{6,P}$ = 18.8, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.4 Hz, 1 H, C(6)-H], 3.11 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.3, $^3J_{4,5}$ = 4.2 Hz, 1 H, C(5)-H], 2.97 [dt, $^1J_{1,P}$ = 22.8, $^3J_{1,6}$ = $^3J_{1,2}$ = 6.0 Hz, 1 H, C(1)-H], 2.72 [dqd, $^2J_{4,4'}$ = 16.3, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 4.0, $^4J_{2,4}$ = 1.0 Hz, 1 H, C(4)-H], 2.25 [dddq, $^2J_{4,4'}$ = 16.3, $^3J_{4',5}$ = 8.3, $^3J_{3,4'}$ = 5.3, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.7 Hz, 1 H, C(4)-H′], 1.56 (tt, ^3J = 7.2, ^3J = 7.0 Hz, 2 H, NCH$_2$CH_2), 1.32 [t, ^3J = 6.9 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.31 [t, ^3J = 6.9 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.28–1.24 [m, 6 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_2$CH$_3$, N(CH$_2$)$_3$CH_2CH$_2$CH$_3$, and N(CH$_2$)$_4$CH_2CH$_3$], 0.87 [t, ^3J = 6.9 Hz, 3 H, N(CH$_2$)$_4$CH$_2$-CH_3] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 4.4 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 124.3 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 63.1 [d, ^2J = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.9 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.7 [d, $^2J_{6,P}$ = 3.4 Hz, C(6)], 39.0 (s, NCH$_2$), 39.0 [d, $^3J_{5,P}$ = 9.0 Hz, C(5)], 34.1 [d, $^1J_{1,P}$ = 146.4 Hz, C(1)], 31.4 [s, N(CH$_2$)$_3$$CH_2CH_2CH_3$], 27.5 (s, NCH$_2$$CH_2$), 26.5 [s, N(CH$_2$)$_2$$CH_2$], 22.9 [s, C(4)], 22.5 [s, N(CH$_2$)$_4$-CH$_2$CH$_3$], 16.4 [d, ^3J = 5.8 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.4 [d, ^3J = 6.0 Hz, PO(OCH$_2$$CH_3$)$_2$], 14.0 [s, N(CH$_2$)$_5$$CH_3$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ = 25.90 ppm. IR: $\tilde{\nu}$ = 2930 (w), 2858 (w), 1778 (w, C=O), 1697 (s, C=O), 1439 (m), 1402 (m), 1254 (m, P=O), 1056 (m), 1024 (s, P–O), 960 (s, P–O), 754 (w) cm^{-1}. MS [APCI (atmospheric pressure chemical ionization), positive mode]: *m*/*z* (%) = 373.12 (19) [M + H], 372.11 (100) [M], 345.12 (2) [M + H – CH$_2$=CH$_2$], 344.11 (13) [M – CH$_2$=CH$_2$], 317.18 (1) [M + H – 2CH$_2$=CH$_2$], 316.16 (6) [M – 2CH$_2$=CH$_2$], 298.04 (1) [M – 2CH$_2$=CH$_2$ – H$_2$O]. HRMS (MALDI-TOF, positive mode): calcd. for C$_{18}$H$_{31}$NO$_5$P (100) [M + H] 372.1940; found 372.1928.

Diethyl 2-(6-Chlorohexyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5b): *N*-(6-Chlorohexyl)maleimide (**3b**, 0.224 g, 1.038 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.198 g, 1.038 mmol) gave **5b** as a yellow oil (244 mg, 58%). R_f = 0.3 (ethyl acetate/acetone, 1:1). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.12–6.05 [m, 1 H, C(3)-H], 6.03–5.95 [m, 1 H, C(2)-H], 4.25–4.11 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.08 [q, ^3J = 6.9 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 3.51 (t, ^3J = 6.7 Hz, 2 H, CH_2Cl), 3.48–3.43 (m, 2 H, NCH_2), 3.32 [ddd, $^3J_{6,P}$ = 18.8, $^3J_{5,6}$ = 9.3, $^3J_{1,6}$ = 6.6 Hz, 1 H, C(6)-H], 3.10 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.2, $^3J_{4,5}$ = 4.2 Hz, 1 H, C(5)-H], 2.97 [dt, $^1J_{1,P}$ = 22.7, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.74–2.65 [m, $^2J_{4,4'}$ = 16.5 Hz, 1 H, C(4)-H], 2.39–2.30 [m, 1 H, C(4)-H′], 1.75 (tt, ^3J = 7.3, ^3J = 6.9 Hz, 2 H, CH_2CH$_2$Cl), 1.57 (quint, ^3J = 7.5 Hz, 2 H, NCH$_2$CH_2), 1.44 [tt, ^3J = 7.7, ^3J = 7.4 Hz, 2 H, N(CH$_2$)$_3$CH_2(CH$_2$)$_2$Cl], 1.36 [tt, ^3J = 7.5, ^3J = 7.0 Hz, 2 H, N(CH$_2$)$_2$-CH_2(CH$_2$)$_3$Cl], 1.31 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.30 [t, ^3J = 6.9 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.30–1.22 [m, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$Cl] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 4.0 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 124.3 [d, $^2J_{2,P}$ = 7.5 Hz, C(2)], 63.1 [d, ^2J = 6.5 Hz, PO(OCH$_2$-CH$_3$)$_2$], 62.0 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 44.9 (s, CH$_2$Cl), 40.7 [d, $^2J_{6,P}$ = 3.1 Hz, C(6)], 38.9 [d, $^3J_{5,P}$ = 9.6 Hz, C(5)], 38.8 (s, NCH$_2$), 34.1 [d, $^1J_{1,P}$ = 146.4 Hz, C(1)], 32.4 (s, CH$_2$CH$_2$Cl), 27.4 (s, NCH$_2$$CH_2$), 26.4 [s, N(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$Cl], 26.1 [s, N(CH$_2$)$_2$-$CH_2$(CH$_2$)$_3$Cl], 22.9 [s, C(4)], 16.4 [d, ^3J = 6.1 Hz, PO(OCH$_2$-CH$_3$)$_2$], 16.4 [d, ^3J = 6.4 Hz, PO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ = 26.10 ppm. IR: $\tilde{\nu}$ = 2988 (m), 2931 (m), 2860 (w), 1776 (m, C=O), 1699 (s, C=O), 1402 (s), 1047 (s), 1228 (m, P=O), 1022 (s, P–O), 960 (s, P–O), 788 (s), 754 (s, C–Cl), 681 (w) cm^{-1}. HRMS (MALDI-TOF, positive mode): calcd. for C$_{18}$H$_{30}$NO$_5$ClP (100) [M + H] 406.1550; found 406.1530; *m*/*z* = 428.1333 (38) [M + Na], 378.1212 (16) [M + H – CH$_2$=CH$_2$], 350.0928 (12) [M + H – 2CH$_2$=CH$_2$].

Diethyl 2-(6-Cyanohexyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5c): *N*-(6-Cyanohexyl)maleimide (**3c**, 0.658 g, 3.19 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.607g, 3.19 mmol) gave **5c** as a yellow oil (0.607 g, 48%), after purification by column chromatography on silica gel (ethyl acetate then acetonitrile). R_f = 0.3 (ethyl acetate). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.12–6.06 [m, 1 H, C(3)-H], 6.02–5.94 [m, 1 H, C(2)-H], 4.24–4.12 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.11–4.04 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 3.49–3.44 (m, 2 H, NCH_2), 3.32 [ddd, $^3J_{6,P}$ = 18.9, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 7.2 Hz, 1 H, C(6)-H], 3.11 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.2, $^3J_{4,5}$ = 4.3 Hz, 1 H, C(5)-H], 2.98 [ddd, $^1J_{1,P}$ = 22.9, $^3J_{1,6}$ = 6.3, $^3J_{1,2}$ = 5.6 Hz, 1 H, C(1)-H], 2.76–2.68 [m, $^2J_{4,4'}$ = 16.4 Hz, 1 H, C(4)-H], 2.40–2.35 [m, 1 H, C(4)-H′], 2.34 (t, ^3J = 7.1 Hz, 2 H, CH_2CN), 1.64 (m, 2 H, NCH$_2$CH_2), 1.64 (tt, ^3J = 7.5, ^3J = 7.3 Hz, 2 H, NCH$_2$CH_2), 1.58 (tt, ^3J = 8.0, ^3J = 7.5 Hz, 2 H, CH_2CH$_2$CN), 1.46 [tt, ^3J = 7.6, ^3J = 7.5 Hz, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$Cl or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$Cl], 1.30 [m, 8 H, PO(OCH$_2$CH_3)$_2$ and N(CH$_2$)$_2$CH_2(CH$_2$)$_3$Cl or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$Cl] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.1 (s, C=O), 176.5 (d, ^3J = 3.6 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 12.2 Hz, C(3)], 124.3 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 119.7 (s, CN), 63.0 [d, ^2J = 6.4 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.9 [d, ^2J = 7.0 Hz, PO(CH$_2$CH$_3$)$_2$], 40.7 [d, $^3J_{6,P}$ = 2.9 Hz, C(6)], 38.8 [d, $^3J_{5,P}$ = 8.8 Hz, C(5)], 38.6 (s, NCH$_2$), 34.0 [d, $^1J_{1,P}$ = 146.0 Hz, C(1)], 28.1 (s, NCH$_2$$CH_2$), 27.2 [s, N(CH$_2$)$_2$$CH_2$], 25.9 [s, N(CH$_2$)$_3$-$CH_2$(CH$_2$)$_3$CN], 25.2 [s, N(CH$_2$)$_4CH_2CH_2$CN], 22.8 [s, C(4)], 17.0 (s, CH$_2$CN), 16.4 [d, ^3J = 6.4 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.3 [d, ^3J = 6.9 Hz, PO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ = 25.98 ppm. IR: $\tilde{\nu}$ = 2970 (m), 2945 (m), 2858 (m), 2243 (w, CN), 1737 (s, C=O), 1708 (s, C=O), 1357 (m), 1217 (s, P=O), 1051 (s), 1024 (s, P–O), 962 (s, P–O), 754 (m) cm^{-1}. HRMS (MALDI-TOF, positive mode): calcd. for C$_{19}$H$_{29}$N$_2$O$_5$NaP (100) [M + Na] 419.1712; found 419.1692.

Diethyl 2-(6-*tert*-Butylhexylcarbamoyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5d): *N*-[*N*′-(*tert*-Butyloxycarbonyl)-6-aminohexyl]maleimide (**3d**, 0.229 g, 0.776 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.147 g, 0.776 mmol) gave **5d** as a yellow oil (256 mg, 68%). R_f = 0.3 (ethyl acetate). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 6.08 [dtt, $^3J_{2,3}$ = 9.3, $^3J_{3,4'}$ = $^4J_{3,5}$ = 4.6, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.7 Hz, 1 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.3, $^3J_{2,P}$ = $^3J_{1,2}$ = 6.0, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.9 Hz, 1 H, C(2)-H], 4.73 (br. s, 1 H, NHBoc), 4.23–4.11 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.07 [q, $^3J'$ = 7.1 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 3.49–3.40 (m, 2 H, NCH_2), 3.31 [ddd, $^3J_{6,P}$ = 19.2, $^3J_{5,6}$ = 9.3, $^3J_{1,6}$ = 6.7 Hz, 1 H, C(6)-H], 3.11 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.3, $^3J_{4,5}$ = 4.3 Hz, 1 H, C(5)-H], 3.07 (t, ^3J = 7.2 Hz, 2 H, CH_2NHBoc), 2.97 [ddd, $^1J_{1,P}$ = 22.6, $^3J_{1,6}$ = 5.9, $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.70 [dqd, $^2J_{4,4'}$ = 16.4, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 4.1, $^4J_{2,4}$ = 1.4 Hz, 1 H, C(4)-H], 2.35 [dddq, $^2J_{4,4'}$ = 16.3, $^3J_{4',5}$ = 8.4, $^3J_{3,4'}$ = 5.4, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.7 Hz, 1 H, C(4)-H′], 1.54 (tt, ^3J = 7.4, ^3J = 7.0 Hz, 2 H, NCH$_2$CH_2), 1.48–1.43 (m, 2 H, CH_2CH$_2$CN), 1.42 [s, 9 H, CH$_3$(Boc)], 1.33–1.26 [m, 10 H, PO(OCH$_2$CH_3)$_2$, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$CN, and N(CH$_2$)$_3$CH_2(CH$_2$)$_2$-CN] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 4.4 Hz, C=O), 156.0 [s, (Boc)C=O], 130.3 [d, $^3J_{3,P}$ = 12.2 Hz, C(3)], 124.2 [d, $^2J_{2,P}$ = 7.8 Hz, C(2)], 78.8 [s, Cq(Boc)], 63.0 [d, ^2J = 6.5 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.8 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.6 [d, $^2J_{6,P}$ = 3.3 Hz, C(6)], 40.3 (s, CH$_2$NHBoc), 38.8 [d, $^3J_{5,P}$ = 8.2 Hz, C(5)], 38.7 (s, NCH$_2$), 33.9 [d, $^1J_{1,P}$ = 146.1 Hz, C(1)], 29.7 (s, CH$_2$CH$_2$NHBoc), 28.4 [s, CH$_3$(Boc)], 27.4 (s, NCH$_2$$CH_2$), 26.3 [s, N(CH$_2$)$_2$$CH_2$(CH$_2$)$_3$-NHBoc or N(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$NHBoc], 26.2 [s, N(CH$_2$)$_3$$CH_2$-(CH$_2$)$_2$NHBoc or N(CH$_2$)$_2$$CH_2$(CH$_2$)$_3$NHBoc], 22.8 [s, C(4)], 16.3 [d, $^3J_{6,P}$ = 6.5 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.3 [d, ^3J = 6.8 Hz, PO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ =

26.15 ppm. IR: ṽ = 2975 (m), 2937 (m), 2856 (w), 1776 (m, C=O), 1693 (s, C=O), 1523 (s), 1402 (s), 1365 (m), 1248 (s, P=O), 1165 (s), 1053 (s), 1024 (s, P–O), 962 (s, P–O), 752 (s), 681 (w) cm^{-1}. HRMS (MALDI-TOF, positive mode): calcd. for $C_{23}H_{39}N_2O_7NaP$ (100) [M + Na] 509.2393; found 509.2380; *m*/*z* = 493.2612 (9) [M + Na – CH_3], 453.1799 (6) [M + Na – 2CH_2=CH_2] or [M + Na – $C(CH_3)_2$], 387.2039 (7) [M + Na – PO(OEt)$_2$].

Diethyl 2-(Hex-5-ynyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5e): *N*-(Hex-5-ynyl)maleimide (**3e**, 66 mg, 0.374 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (71 mg, 0.374 mmol) gave **5e** as a brown oil (63 mg, 46%). R_f = 0.3 (ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.12–6.04 [m, 1 H, C(3)-H], 6.02–5.93 [m, 1 H, C(2)-H], 4.22–4.11 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.10–4.01 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 3.47 (m, 2 H, NCH_2), 3.31 [ddd, $^3J_{6,P}$ = 19.3, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.9 Hz, 1 H, C(6)-H], 3.11 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.1, $^3J_{4,5}$ = 4.2 Hz, 1 H, C(5)-H], 2.97 [dt, $^1J_{1,P}$ = 22.5, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.74–2.65 [dt, $^2J_{4,4'}$ = 16.3, $^3J_{3,4}$ = $^3J_{4,5}$ = 4.3 Hz, 1 H, C(4)-H], 2.43–2.31 [m, 1 H, C(4)-H′], 2.19 [dt, ^3J = 6.4, ^4J = 3.4 Hz, 2 H, N(CH$_2$)$_3$CH_2], 2.19 [t, ^4J = 3.2 Hz, 1 H, CH(alkyne)], 1.74–1.64 (m, 2 H, NCH$_2$CH_2), 1.52–1.46 [m, 2 H, N(CH$_2$)$_2$CH_2], 1.30 [t, ^3J = 6.6 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.28 [t, ^3J = 6.5 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 176.4 (d, $^3J_{9,P}$ = 3.5 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 12.2 Hz, C(3)], 124.2 [d, $^2J_{2,P}$ = 7.5 Hz, C(2)], 83.7 [s, Cq(alkyne)], 68.7 [s, CH(alkyne)], 63.0 [d, ^2J = 6.3 Hz, PO(OCH_2CH$_3$)$_2$], 61.8 [d, ^2J = 7.0 Hz, PO(OCH_2CH$_3$)$_2$], 40.6 [d, $^2J_{6,P}$ = 2.6 Hz, C(6)], 38.8 [d, $^3J_{5,P}$ = 8.7 Hz, C(5)], 38.3 (s, NCH_2), 33.9 [d, $^1J_{1,P}$ = 146.2 Hz, C(1)], 26.6 (s, NCH$_2$CH_2), 25.5 [s, N(CH$_2$)$_2$CH_2], 22.8 [s, C(4)], 17.9 [s, N(CH$_2$)$_3$-CH_2], 16.3 [d, ^3J = 6.3 Hz, PO(OCH$_2$CH_3)$_2$], 16.3 [d, ^3J = 6.6 Hz, PO(OCH$_2$CH_3)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.09 ppm. IR: ṽ = 3226 (w, CH alkyne), 2995 (m), 2941 (m), 2864 (m), 2112 (w, CCH alkyne), 1776 (w, C=O), 1695 (s, C=O), 1402 (s), 1226 (P=O, m), 1047 (s), 1020 (P–O, s), 960 (P–O, s), 680 (w) cm^{-1}. HRMS (MALDI-TOF, positive mode): calcd. for $C_{18}H_{26}NO_5NaP$ (100) [M + Na] 390.1446; found 390.1438.

General Procedure for Cycloaddition to 1-Diethoxyphosphoryl-1,3-butadiene (Method B): A neat mixture of the diene (1 equiv.) and *N*-substituted maleimide (1 equiv.) was vigorously stirred at 120 °C for 5–7 h. The advancement of the reaction was controlled by TLC and NMR (^{1}H NMR with the evolution of the dienyl multiplet and ^{31}P NMR with the apparition of the cycloadduct peak). Heating in a microwave oven gave the same results (100 °C, 600 W). The reaction mixture was directly purified by column chromatography on silica gel.

Diethyl 2-(6-Hydroxyhexyl)-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5g): *N*-(6-Hydroxyhexyl)maleimide (**3g**, 0.104 g, 0.530 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.101 g, 0.530 mmol) gave **5g** as a colorless oil (0.114 g, 56%). R_f = 0.3 (ethyl acetate/acetone, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.07 [dtt, $^3J_{2,3}$ = 9.3, $^3J_{3,4'}$ = $^4J_{3,5}$ = 5.8, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.4 Hz, 1 H, C(3)-H], 5.96 [dtt, $^3J_{2,3}$ = 9.3, $^3J_{2,P}$ = $^3J_{1,2}$ = 4.7, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.7 Hz, 1 H, C(2)-H], 4.20–4.12 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.12–4.02 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 3.58 (br. t, ^3J = 6.5 Hz, 2 H, CH_2OH), 3.44 (br. t, ^3J = 6.4 Hz, 2 H, NCH_2), 3.30 [ddd, $^3J_{6,P}$ = 18.9, $^3J_{5,6}$ = 9.5, $^3J_{1,6}$ = 6.6 Hz, 1 H, C(6)-H], 3.08 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.2, $^3J_{4,5}$ = 4.5 Hz, 1 H, C(5)-H], 2.95 [dt, $^3J_{1,P}$ = 22.7, $^3J_{1,2}$ = $^3J_{1,6}$ = 6.0 Hz, 1 H, C(1)-H], 2.77 (br. s, OH), 2.83 [dqd, $^2J_{4,4'}$ = 16.5, $^3J_{3,4}$ = $^3J_{4,6}$ = $^5J_{4,P}$ = 4.5, $^4J_{2,4}$ = 1.0 Hz, 1 H, C(4)-H], 2.33 [dddq, $^2J_{4,4'}$ = 16.3, $^3J_{4',5}$ = 9.1, $^3J_{3,4'}$ = 5.3, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.8 Hz, 1 H, C(4)-H′], 1.58–1.48 (m, 4 H, NCH$_2$CH_2 and CH_2CH$_2$OH), 1.38–1.30 (m, 4 H, NCH$_2$CH$_2$CH_2 and CH_2CH$_2$CH$_2$OH), 1.29 [t, ^3J = 7.1 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.28 [t, ^3J = 6.6 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.3 (s, C=O), 176.5 (d, ^3J = 4.3 Hz, C=O), 130.4 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 124.2 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 63.1 [d, ^2J = 6.5 Hz, PO(OCH_2CH$_3$)$_2$], 62.2 (s, CH_2OH), 62.0 [d, ^2J = 7.0 Hz, PO(OCH_2CH$_3$)$_2$], 40.6 [d, $^2J_{6,P}$ = 3.1 Hz, C(6)], 38.8 [d, $^3J_{5,P}$ = 8.3 Hz, C(5)], 38.8 (s, NCH_2), 33.9 [d, $^1J_{1,P}$ = 146.4 Hz, C(1)], 32.4 (s, CH_2CH$_2$OH), 27.5 [s, C(4)], 26.3 (s, NCH$_2$CH_2), 25.2 (s, NCH$_2$CH$_2$CH_2), 22.9 (s, CH_2CH$_2$CH$_2$OH), 16.3 [d, ^3J = 6.6 Hz, PO(OCH$_2$CH_3)$_2$], 16.3 [d, ^3J = 6.8 Hz, PO(OCH$_2$CH_3)$_2$] ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 25.96 ppm. IR: ṽ = 3743–3087 (br. m, OH), 2982 (m), 2931 (m), 2860 (m), 1776 (w, C=O), 1697 (s, C=O), 1649 (w), 1441 (m), 1402 (s), 1367 (m), 1348 (m), 1225 (s, P=O), 1049 (m), 1020 (s, P–O), 964 (s, P–O), 791 (w), 752 (w) cm^{-1}. MS (APCI, positive mode): *m*/*z* (%) = 389.05 (17) [M + H], 388.03 (100) [M], 370.10 (6) [M – H_2O], 360.12 (10) [M – CH_2=CH_2], 342.09 (13) [M – CH_2=CH_2 – H_2O], 332.15 (1) [M – 2CH_2=CH_2], 314.14 (15) [M – 2 CH_2=CH_2 – H_2O], 297.12 (6) [M + H-2 CH_2=CH_2 – 2 H_2O], 269.15 (3) [M + H-3 CH_2=CH_2 – H_2O], 232.16 (5) [M – 2 CH_2=CH_2-(CH$_2$)$_5$OH]. HRMS (MALDI-TOF, positive mode): calcd. for $C_{18}H_{30}NO_6PNa$ [M + Na] 410.1703; found 410.1697.

Diethyl 2-[(5-Hydroxyethoxy)ethyl]-1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate (5h): *N*-[2-(2-Hydroxyethoxy)ethyl]maleimide (**3h**, 0.209 g, 1.99 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.378 g, 1.99 mmol) furnished **5h** as a yellow oil (0.25 g, 28%). R_f = 0.3 (ethyl acetate/acetone, 1:2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.15–6.09 [m, 1 H, C(3)-H], 5.98 [apparent q, $^3J_{2,3}$ = 7.9 Hz, 1 H, C(2)-H], 4.18–4.05 [m, 4 H, PO(OCH_2-CH$_3$)$_2$], 3.72 (t, ^3J = 6.1 Hz, 1 H, CH_2OH), 3.69 (t, ^3J = 5.2 Hz, 1 H, CH_2OH), 3.66–3.61 (m, 4 H, CH_2OCH_2), 3.54 (t, ^3J = 4.3 Hz, 2 H, CH_2N), 3.34 [ddd, $^3J_{6,P}$ = 20.2, $^3J_{5,6}$ = 9.2, $^4J_{1,6}$ = 6.9 Hz, 1 H, C(6)-H], 3.16 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = 4.9 Hz, 1 H, C(5)-H], 3.04 [ddd, $^1J_{1,P}$ = 22.6, $^3J_{1,6}$ = 6.2, $^3J_{1,2}$ = 6.1 Hz, 1 H, C(1)-H], 2.72 [dq, $^3J_{4,4'}$ = 16.4, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 4.4 Hz, 1 H, C(4)-H], 2.44–2.40 [ddd, $^3J_{4',4}$ = 15.0, $^4J_{4,5}$ = 7.5, $^3J_{3,4'}$ = 7.4 Hz, 1 H, C(4)-H′], 1.32 [t, ^3J = 6.2 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.31 [t, ^3J = 6.2 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.9 (s, C=O), 176.3 (d, ^3J = 4.9 Hz, C=O), 130.0 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 123.7 [d, $^2J_{2,P}$ = 7.9 Hz, C(2)], 72.2 (s, CH_2OH), 67.0 (s, NCH$_2$CH_2O), 62.7 [d, ^2J = 6.7 Hz, PO(OCH_2CH$_3$)$_2$], 61.8 [d, ^2J = 7.1 Hz, PO(OCH_2CH$_3$)$_2$], 61.1 (s, OCH_2CH$_2$OH), 40.2 [d, $^2J_{6,P}$ = 3.0 Hz, C(6)], 38.5 [d, $^3J_{5,P}$ = 8.4 Hz, C(5)], 38.2 (s, NCH_2), 33.6 [d, $^1J_{1,P}$ = 145.8 Hz, C(1)], 22.4 [s, C(4)], 16.1 [d, ^3J = 6.3 Hz, PO(OCH$_2$CH_3)$_2$], 16.0 [d, ^3J = 6.5 Hz, PO(OCH$_2$CH_3)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.90 ppm. IR: ṽ = 3697–3386 (large band, m, OH), 2982 (m), 2933 (m), 2918 (m), 1776 (w, C=O), 1703 (s, C=O), 1728 (w), 1441 (w), 1398 (s), 1229 (s, P=O), 1128 (m), 1051 (s), 1020 (s, P–O), 959 (s, P–O), 791 (w), 752 (w), 681 (s) cm^{-1}. MS (APCI, positive mode): *m*/*z* (%) = 376.11 (100) [M + H], 348.13 (6) [M – CH_2=CH_2]. HRMS (ESI, positive mode): calcd. for $C_{16}H_{26}NO_7PNa$ [M + Na] 398.13391; found 398.13366; calcd. for $C_{16}H_{26}NO_7PK$ [M + K] 414.10843; found 414.10718; calcd. for $C_{32}H_{52}N_2O_{14}P_2Na$ [2M + Na]$^+$ 773.27291; found 773.27872.

General Procedure for Bis-Cycloaddition: A mixture of the diene (2 equiv.) and bis(maleimide) **3i**–**3j** (1 equiv.) was vigorously stirred at 140 °C for 5–7 h. The advancement of the reaction was controlled by TLC and NMR. The reaction mixture was directly purified by column chromatography on silica gel.

Diethyl 2,2′-Hexane-1,6-diylbis(1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate) (5i): *N*,*N*-Hexamethylenebis(maleimide) (**3i**, 0.36 g, 1.32 mmol) and 1-diethoxyphosphoryl-1,3-buta-

diene (0.50 g, 2.63 mmol) furnished **5i** as a yellow oil (0.13 g, 16%), after purification by column chromatography on silica gel (ethyl acetate then ethyl acetate/MeOH, 9:1). R_f = 0.3 (ethyl acetate/MeOH, 9:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 [dtt, $^3J_{2,3}$ = 9.2, $^3J_{3,4}$ = $^4J_{3,5}$ = 4.6, $^3J_{3,4'}$ = $^4J_{3,P}$ = 1.5 Hz, 2 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.0, $^3J_{2,P}$ = $^3J_{1,2}$ = 5.8, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.1 Hz, 2 H, C(2)-H], 4.21–4.12 [4 H, m PO(OCH_2CH$_3$)$_2$], 4.12–4.04 [m, 4 H, PO(OCH_2CH$_3$)$_2$], 3.43 [m, 4 H, NCH_2(CH$_2$)$_4$CH_2N], 3.33 [ddd, $^3J_{6,P}$ = 18.4, $^3J_{5,6}$ = 9.1, $^3J_{1,6}$ = 6.9 Hz, 2 H, C(6)-H], 3.12 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = 4.2 Hz, 2 H, C(5)-H], 2.96 [dt, $^1J_{1,P}$ = 22.7, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.8 Hz, 2 H, C(1)-H], 2.70 [dq, $^2J_{4,4'}$ = 16.3, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 3.9 Hz, 2 H, C(4)-H], 2.34 [dddq, $^2J_{4,4'}$ = 16.3, $^3J_{4',5}$ = 8.9, $^3J_{3,4'}$ = 5.5, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.7 Hz, 2 H, C(4)-H′], 1.53 [tt, ^3J = 7.1, ^3J = 6.7 Hz, 4 H, NCH$_2$CH_2(CH$_2$)$_2$CH_2CH$_2$N], 1.31 [t, ^3J = 7.2 Hz, 6 H, PO(OCH$_2$CH_3)$_2$], 1.30 [t, ^3J = 7.1 Hz, 6 H, PO(OCH$_2$CH_3)$_2$], 1.25 (t, ^3J = 7.2 Hz, 4 H, NCH$_2$CH$_2$-CH_2CH$_2$CH$_2$CH$_2$N) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 176.4 (d, ^3J = 4.3 Hz, C=O), 130.2 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 124.1 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 62.9 [d, ^2J = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.8 [d, $^2J_5$ = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.5 [d, $^2J_{6,P}$ = 3.2 Hz, C(6)], 38.7 [d, $^3J_{5,P}$ = 10.7 Hz, C(5)], 38.7 [s, NCH$_2$(CH$_2$)$_4$CH$_2$N], 33.8 [d, $^1J_{1,P}$ = 146.4 Hz, C(1)], 27.2 [s, NCH$_2$CH$_2$(CH$_2$)$_2$CH$_2$CH$_2$N], 26.2 (s, NCH$_2$CH$_2$CH$_2$CH$_2$CH$_2$-CH$_2$N), 22.8 [s, C(4)], 16.3 [d, ^3J = 6.2 Hz, PO(OCH$_2$CH$_3$)$_2$], 16.2 [d, ^3J = 6.4 Hz, PO(OCH$_2$CH$_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 25.95 ppm. IR: $\tilde{\nu}$ = 2985 (w), 2926 (w), 2858 (w), 1776 (w, C=O), 1695 (s, C=O), 1441 (m), 1402 (s), 1247 (w, P=O), 1055 (w), 1020 (m, P–O), 962 (s, P–O), 752 (s) cm^{-1}. MS (ESI, positive mode): *m/z* (%) = 680.26 (32) [M + H + Na], 679.26 (100) [M + Na], 657.06 (33) [M + H], 629.13 (16) [M + H-CH$_2$=CH$_2$], 601.14 (11) [M + H-2 CH$_2$=CH$_2$]. HRMS (ESI, positive mode): calcd. for $C_{30}H_{46}N_2O_{10}P_2Na$ (100) [M + Na] 679.25199; found 679.25208; calcd. for $C_{30}H_{47}N_2O_{10}P_2$ (3) [M + H] 657.2705; found 657.2707.

Diethyl 2,2′-(Oxydiethane-2,1-diyl)bis(1,3-dioxo-2,3,3a,4,7,7a-hexahydro-1*H*-isoindole-4-phosphonate) (5j): *N*,*N*-(Oxydiethane-2,1-diyl)bis(maleimide) (**3j**, 0.246 g, 1.00 mmol) and 1-diethoxyphosphoryl-1,3-butadiene (0.380 g, 2.00 mmol) furnished **5j** as a yellow oil (0.11 g, 17%), after purification by column chromatography on silica gel (ethyl acetate then MeOH). R_f = 0.2 (ethyl acetate); R_f = 0.8 (MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09 [dtt, $^3J_{2,3}$ = 9.3, $^3J_{3,4'}$ = $^4J_{3,5}$ = 4.7, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.4 Hz, 2 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.4, $^3J_{2,P}$ = $^3J_{1,2}$ = 5.0, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.7 Hz, 2 H, C(2)-H], 4.19–4.03 [m, 8 H, PO(OCH_2CH$_3$)$_2$], 3.65–3.53 (m, 8 H, NCH_2CH$_2$OCH$_2$CH_2N), 3.38 [ddd, $^3J_{6,P}$ = 20.4, $^3J_{5,6}$ = 9.3, $^3J_{1,6}$ = 6.3 Hz, 1 H, C(6)-H], 3.35 [ddd, $^3J_{6bis,P}$ = 20.4, $^3J_{5bis,6bis}$ = 9.3, $^3J_{1,6bis}$ = 6.3 Hz, 1 H, C(6bis)-H], 3.24 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.4, $^3J_{4,5}$ = 4.3 Hz, 1 H, C(5)-H], 3.23 [td, $^3J_{4',5bis}$ = $^3J_{5,6bis}$ = 9.3, $^3J_{4,6bis}$ = 4.4 Hz, 1 H, C(6bis)-H], 2.99 [dt, $^1J_{1,P}$ = 22.6, $^3J_{1,6}$ = $^3J_{1,2}$ = 6.0 Hz, 2 H, C(1)-H], 2.71 [dqd, $^2J_{4,4'}$ = 16.5, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 4.3, ^4J = 2 Hz, 2 H, or $^4J_{4,6}$ or $^5J_{1,4}$ = 1.5 Hz, C(4)-H], 2.35 [dddq, $^2J_{4,4'}$ = 16.2, $^3J_{4',5}$ = 9.0, $^3J_{3,4'}$ = 5.3, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.8 Hz, 1 H, C(4)-H′], 1.30 [t, ^3J = 7.1 Hz, 6 H, PO(OCH$_2$CH_3)$_2$], 1.29 [t, ^3J = 7.1 Hz, 6 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 179.0 (s, C=O), 176.4 (d, ^3J = 3.7 Hz, C=O), 176.4 (d, ^3J = 3.9 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 5.7 Hz, C(3)], 130.2 [d, $^3J_{3bis,P}$ = 5.8 Hz, C(3bis)], 123.7 [d, $^2J_{2,P}$ = 5.8 Hz, C(2)], 123.7 [d, $^2J_{2bis,P}$ = 5.8 Hz, C(2bis)], 66.4 (s, NCH$_2$CH_2OCH$_2$CH$_2$N), 62.8 [d, ^2J = 6.4 Hz, PO(OCH$_2$CH$_3$)$_2$], 62.7 [d, ^2J = 6.4 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.7 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.5 [d, $^2J_{6,P}$ = 4.2 Hz, C(6)], 40.4 [d, $^2J_{6bis,P}$ = 4.1 Hz, C(6bis)], 38.5 [d, $^3J_{5,P}$ = 8.5 Hz, C(5)], 38.4 [d, $^3J_{5bis,P}$ = 8.6 Hz, C(5bis)], 33.8 [d, $^1J_{1,P}$ = 145.3 Hz, C(1)], 22.5 [s, C(4)], 16.2 [d, ^3J = 6.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 16.1 [d, ^3J = 6.1 Hz, PO(OCH$_2$CH$_3$)$_2$] ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 25.90 and 26.87 ppm. IR: $\tilde{\nu}$ = 2986 (w), 2908 (w), 1776 (w, C=O), 1697 (s, C=O), 1441 (m), 1398 (s), 1339 (s), 1130 (m), 1014 (m, P–O), 957 (s, P–O), 748 (s) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{28}H_{42}N_2O_{11}P_2Na$ (100) [M + Na] 667.21560; found 667.21526; calcd. for $C_{28}H_{43}N_2O_{11}P_2$ (13) [M + H] 645.23366; found 645.23369.

General Procedure for Acylation of Alcohol 5g: In a flame-dried flask, **5g** (1.0 equiv.) was dissolved in anhydrous dichloromethane (2 mL per 0.3 mmol of **5g**). The acylation agent (1.0 equiv.) and triethylamine (2.2 equiv.) were added successively. The mixture was stirred and heated at reflux, and the reaction was followed by TLC. If needed, the acylation agent and triethylamine were added again in the same proportions as before. After 3–8 h, water was added, and the organic phase was recovered. The aqueous layer was extracted (4×) with dichloromethane, and the combined organic layers were dried with magnesium sulfate. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel (ethyl acetate/acetone, 1:1).

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 6: Compound **5g** (118 mg, 0.31 mmol), methyl malonyl chloride (32.7 μL, 41.6 mg, 0.30 mmol), and triethylamine (64.6 μL, 67.7 mg, 0.67 mmol) in dichloromethane (2 mL), gave **6** as a yellow oil (108 mg, 73%). R_f = 0.4 (ethyl acetate/acetone, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.08 [dtt, $^3J_{2,3}$ = 9.2, $^3J_{3,4}$ = $^4J_{1,3}$ = 4.7, $^3J_{3,4'}$ = $^4J_{3,P}$ = 1.5 Hz, 1 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.0, $^3J_{2,P}$ = $^3J_{1,2}$ = 6.2, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.4 Hz, 1 H, C(2)-H], 4.18 [q, ^3J = 7.1 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 4.11 [t, ^3J = 6.7 Hz, 2 H, N(CH$_2$)$_5$CH_2OCO], 4.08 [q, ^3J = 7.1 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 3.74 (s, 3 H, CO$_2$CH_3), 3.45 [m, 2 H, NCH_2(CH$_2$)$_5$O], 3.37 (s, 2 H, COCH_2CO), 3.33 [ddd, $^2J_{6,P}$ = 18.7, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.5 Hz, 1 H, C(6)-H], 3.10 [dt, $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = $^3J_{4',5}$ = 4.2 Hz, 1 H, C(5)-H], 2.96 [dt, $^1J_{1,P}$ = 22.8, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.71 [dq, $^2J_{4,4'}$ = 16.3, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 4.2 Hz, 1 H, C(4)-H], 2.34 [dddq, $^2J_{4,4'}$ = 16.2, $^3J_{4',5}$ = 9.0, $^3J_{3,4'}$ = 5.3, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.8 Hz, 1 H, C(4)-H′], 1.62 [tt, ^3J = 7.2, ^3J = 6.8 Hz, 2 H, N(CH$_2$)$_4$CH_2CH$_2$O], 1.55 [quint, ^3J = 7.4 Hz, 2 H, NCH$_2$CH_2(CH$_2$)$_4$O], 1.35 [tt, J = 7.3, J = 7.7 Hz, 2 H, N(CH$_2$)$_3$-CH_2(CH$_2$)$_2$O or N(CH$_2$)$_2$CH_2(CH$_2$)$_3$O], 1.32–1.27 [m, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$O or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$O], 1.31 [t, ^3J = 6.1 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.29 [t, ^3J = 6.8 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2 (s, C=O), 176.6 (d, ^3J = 4.3 Hz, C=O), 167.1 (s, C=O), 166.6 (s, C=O), 130.4 [d, ^3J = 12.4 Hz, C(3)], 124.3 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 65.5 (s, *C*H$_2$OCOCH$_2$CO), 63.2 [d, ^2J = 6.6 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 62.0 [d, ^2J = 7.0 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 52.6 (s, CO$_2$*C*H$_3$), 41.4 (s, CO*C*H$_2$CO), 40.7 [d, $^2J_{6,P}$ = 3.4 Hz, C(6)], 38.9 [d, $^3J_{5,P}$ = 10.9 Hz, C(5)], 38.9 [s, N*C*H$_2$(CH$_2$)$_5$O], 34.0 [d, $^1J_{1,P}$ = 146.6 Hz, C(1)], 28.3 [s, N(CH$_2$)$_4$*C*H$_2$CH$_2$O], 27.5 [s, NCH$_2$*C*H$_2$(CH$_2$)$_4$O], 26.4 [s, N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$O or N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$O], 25.4 [s, (CH$_2$)$_2$-*C*H$_2$(CH$_2$)$_3$O or N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$O], 22.9 [s, C(4)], 16.4 [d, ^3J = 6.2 Hz, PO(OCH$_2$*C*H$_3$)$_2$], 16.4 [d, ^3J = 6.5 Hz, PO(OCH$_2$-*C*H$_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.22 ppm. IR: $\tilde{\nu}$ = 2932 (m), 1732 (s, C=O), 1699 (C=O, s), 1438 (s), 1402 (m), 1255 (w, P=O), 1151 (m), 1020 (s, P–O), 959 (s, P–O), 788 (m) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{22}H_{35}NO_9P$ (100) [M + H] 488.20439; found 488.20285; *m/z* = 511.18832 (80) [M + H + Na]; calcd. for $C_{44}H_{68}N_2O_{18}P_2Na$ (11) [2M + Na] 997.38346; found 997.38275.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 7: Compound **5g** (124.5 g, 0.32 mmol), picolinoyl hydrochloride (57.2 mg, 0.32 mmol), and triethylamine (95 μL, 71.5 mg, 0.71 mmol) in dichloromethane (2 mL) gave **7** as a yellowish oil (104 mg, 66%).

R_f = 0.4 (ethyl acetate/acetone, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.77 (dq, ^3J = 4.8, J = 0.8 Hz, 1 H, CH pyridine), 8.13 (d, ^3J = 7.9 Hz, 1 H, CH pyridine), 7.85 (td, ^3J = 7.7, ^4J = 1.7 Hz, 1 H, CH pyridine), 7.48 (ddd, ^3J = 7.4, ^3J = 4.8, ^4J = 1.1 Hz, 1 H, CH pyridine), 6.08 [dtt, $^3J_{2,3}$ = 10.0, $^3J_{3,4'}$ = $^4J_{3,5}$ = 4.4, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.6 Hz, 1 H, C(3)-H], 6.00 [dtt, $^3J_{2,3}$ = 9.4, $^3J_{2,P}$ = $^3J_{2,6}$ = 5.1, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.6 Hz, 1 H, C(2)-H], 4.40 [t, ^3J = 6.8 Hz, 2 H, CH_2OCO(C_5H_4N)], 4.22–4.12 [m, 2 H, PO(CH_2CH$_3$)$_2$], 4.08 [q, ^3J = 7.2 Hz, 2 H, PO(CH_2CH$_3$)$_2$], 3.47 (m, 2 H, NCH_2), 3.32 [ddd, $^3J_{6,P}$ = 19.0, $^3J_{5,6}$ = 9.3, $^3J_{1,6}$ = 6.4 Hz, 1 H, C(6)-H], 3.10 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.3, $^3J_{4,5}$ = 4.3 Hz, 1 H, C(5)-H], 2.97 [dt, $^1J_{1,P}$ = 22.7, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.9 Hz, 1 H, C(1)-H], 2.72 [dq, $^2J_{4,4'}$ = 16.4, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 4.2 Hz, 1 H, C(4)-H], 2.35 [dddq, $^2J_{4,4'}$ = 16.4, $^3J_{4',5}$ = 9.1, $^3J_{3,4'}$ = 5.4, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.8 Hz, 1 H, C(4)-H′], 1.81 (tt, ^3J = 7.4, ^3J = 7.1 Hz, 2 H, CH_2CH$_2$OCO), 1.59 (tt, ^3J = 7.6, ^3J = 7.5 Hz, 2 H, NCH$_2$CH_2), 1.46 [quint, J = 7.6 Hz, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$OCO or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$OCO], 1.38–1.33 [m, 2 H, N(CH$_2$)$_3$CH_2(CH$_2$)$_2$OCO or N(CH$_2$)$_2$CH_2(CH$_2$)$_3$OCO], 1.31 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.30 [t, ^3J = 7.1 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.1 (s, C=O), 176.5 (d, ^3J = 4.3 Hz, C=O), 165.2 [s, OCO(C_5H_4N)], 149.9 (s, CH pyridine), 148.2 (s, Cq pyridine), 137.0 (s, CH pyridine), 130.3 [d, $^3J_{3,P}$ = 12.5 Hz, C(3)], 126.8 (s, CH pyridine), 125.1 (s, CH pyridine), 124.2 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 65.8 [s, CH$_2$OC-O(C_5H_4N)], 63.0 [d, ^2J = 6.6 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.9 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.6 [d, $^2J_{6,P}$ = 3.2 Hz, C(6)], 38.8 [d, $^3J_{5,P}$ = 4.4 Hz, C(5)], 38.8 (s, NCH$_2$), 34.0 [d, $^1J_{1,P}$ = 146.2 Hz, C(1)], 28.5 (s, CH$_2$CH$_2$OCO), 27.4 (s, NCH$_2$$CH_2$), 26.4 [s, N(CH$_2$)$_2$-$CH_2$], 25.5 [s, CH$_2$(CH$_2$)$_2$OCO], 22.8 [s, C(4)], 16.4 [d, ^3J = 6.3 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.3 [d, ^3J = 6.5 Hz, PO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.14 ppm. IR: $\tilde{\nu}$ = 2941 (m), 1776 (w, C=O), 1737 (m, C=O), 1699 (s, C=O), 1548 (w), 1246 (m, P=O), 1026 (s, P–O), 960 (s, P–O), 708 (w) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{24}H_{34}N_2O_7P$ (100) [M + H] 493.20981; found 493.20717; m/z = 515.18914 (15) [M + Na]; calcd. for $C_{48}H_{66}N_4O_{14}P_2Na$ (6) [2M + Na] 1007.39430; found 1007.39069.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 9: In a flame-dried flask, **5g** (0.15 g, 0.39 mmol) was dissolved in anhydrous dichloromethane (2 mL). Diethyl chlorophosphonate (0.123 mL, 0.146 g, 0.85 mmol) and triethylamine (0.115 mL, 86 mg, 0.851 mmol) were added successively. The mixture was stirred and heated at reflux overnight. Water was added, and the organic layer was separated. The aqueous layer was extracted (4×) with ethyl acetate, and the combined organic layers were dried with magnesium sulfate. Evaporation of the solvent gave a yellow oil, which was purified by column chromatography on silica gel (ethyl acetate/acetone, 1:1) to give **9** as a yellow oil (104 mg, 51%). R_f = 0.2 (ethyl acetate/acetone, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.10–6.05 [m, 1 H, C(3)-H], 6.02–5.94 [m, 1 H, C(2)-H], 4.16 [q, ^3J = 8.0 Hz, 2 H, OPO(OCH$_2$CH$_3$)$_2$], 4.10 [apparent sextet, ^3J = 7.2 Hz, 6 H, CHPO(OCH$_2$CH$_3$)$_2$ and CH_2OPO(OCH$_2$CH$_3$)], 3.99 [q, ^3J = 6.8 Hz, 2 H, OPO(OCH$_2$CH$_3$)$_2$], 3.43 (m, 2 H, NCH_2), 3.31 [ddd, $^3J_{6,P1}$ = 19.0, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 8.1 Hz, 1 H, C(6)-H], 3.09 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 8.9, $^3J_{4,5}$ = 3.5 Hz, 1 H, C(5)-H], 2.96 [ddd, $^1J_{1,P1}$ = 22.9, $^3J_{1,6}$ = 5.2, $^3J_{1,2}$ = 5.0 Hz, 1 H, C(1)-H], 2.71 [dq, $^2J_{4,4'}$ = 16.5, $^3J_{4,5}$ = $^3J_{3,4}$ = 5.5 Hz, 1 H, C(4)-H], 2.39–2.30 [m, 1 H, C(4)-H′], 1.65 (tt, ^3J = 7.0, ^3J = 6.9 Hz, 2 H, CH_2CH$_2$O), 1.55 (tt, ^3J = 7.0, ^3J = 6.8 Hz, 2 H, NCH$_2$CH_2), 1.38 [m, 2 H, N(CH$_2$)$_2$-CH_2(CH$_2$)$_3$O or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$O], 1.32 [t, ^3J = 7.5 Hz, 6 H, CHPO(OCH_2CH$_3$)$_2$], 1.30 [t, ^3J = 8.0 Hz, 8 H, OPO(OCH$_2$CH_3)$_2$ and N(CH$_2$)$_2$CH_2(CH$_2$)$_3$O or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$O] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 3.5 Hz, C=O), 130.3 [d, $^3J_{3,P1}$ = 12.3 Hz, C(3)], 124.3 [d, $^2J_{2,P1}$ = 7.5 Hz, C(2)], 67.5 [d, ^2J = 5.9 Hz, OPO(OCH$_2$CH$_3$)$_2$], 63.7 [d, ^2J = 5.7 Hz, OPO(OCH$_2$CH$_3$)$_2$], 63.1 [d, ^2J = 6.4 Hz, CH$_2$OPO-(OCH$_2$CH$_3$)$_2$], 62.0 [d, ^2J = 7.0 Hz, PO(OCH$_2$CH$_3$)$_2$], 40.7 [d, $^2J_{6,P1}$ = 2.8 Hz, C(6)], 38.9 [d, $^3J_{5,P1}$ = 9.5 Hz, C(5)], 38.9 (s, NCH$_2$), 34.1 [d, $^1J_{1,P1}$ = 146.0 Hz, C(1)], 30.2 [d, $^3J_{15,P2}$ = 6.8 Hz, CH$_2$CH$_2$O-PO(OCH$_2$CH$_3$)$_2$], 27.5 (s, NCH$_2$$CH_2$), 26.4 (s, NCH$_2CH_2$$CH_2$), 25.1 [s, N(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$O], 22.9 [s, C(4)], 16.4 [d, ^3J = 6.3 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.4 [d, ^3J = 6.3 Hz, PO(OCH$_2$CH$_3$)$_2$], 16.2 [d, ^3J = 6.5 Hz, OPO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.11 [PO(OEt)$_2$] and –0.19 [OPO(OEt)$_2$] ppm. IR: $\tilde{\nu}$ = 2988 (m), 2932 (m), 2862 (m), 1772 (w, C=O), 1701 (s, C=O), 1402 (m), 1259 (m, P=O), 1163 (w), 1027 (s, P–O), 966 (m, P–O), 750 (w), 683 (w) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{22}H_{39}NO_9P_2Na$ (100) [M + Na] 546.19923; found 546.19284; calcd. for $C_{44}H_{78}N_2O_{18}P_4Na$ (62) [2M + Na] 1069.40923; found 1069.40894.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 10: In a flame-dried flask, **5g** (119.0 mg, 0.282 mmol, 1.0 equiv.) was dissolved in anhydrous tetrahydrofuran (2 mL). This solution was cooled to –78 °C. DEAD (57.9 μL, 58.8 mg, 0.338 mmol, 1.1 equiv.), polymer-supported triphenylphosphane (112.6 mg, 0.338 mmol, 1.1 equiv.), and phthalimide (Ft, 45.0 mg, 0.307 mmol, 1 equiv.) were successively added at –78 °C. The mixture was stirred at –78 °C for 30 min and then heated at reflux overnight. The polymer-supported reagent was removed by filtration and rinsed with tetrahydrofuran. Evaporation of the solvent gave an oil, which was purified by column chromatography on silica gel (ethyl acetate/acetone, 1:1) to give **10** as a yellowish oil (53.8 mg, 37%). R_f = 0.5 (ethyl acetate/acetone, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.11–6.45 [m, 1 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.4, $^3J_{2,P}$ = $^3J_{1,2}$ = 5.8, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.5 Hz, 1 H, C(2)-H], 4.22–4.10 [m, 2 H, PO(OCH$_2$CH$_3$)$_2$], 4.07 [q, ^3J = 7.2 Hz, 2 H, PO(OCH$_2$CH$_3$)$_2$], 3.65 (t, ^3J = 7.2 Hz, 2 H, CH_2NFt), 3.47–3.41 (m, 2 H, N CH_2), 3.32 [ddd, $^3J_{6,P}$ = 18.1, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.8 Hz, 1 H, C(6)-H], 3.10 [dt, $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = $^3J_{4',5}$ = 4.2 Hz, 1 H, C(5)-H], 2.96 [dt, $^1J_{1,P}$ = 22.6, $^3J_{1,6}$ = $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.70 [dq, $^2J_{4,4'}$ = 16.5, $^3J_{3,4}$ = $^3J_{4,5}$ = $^5J_{4,P}$ = 2.0 Hz, 1 H, C(4)-H], 2.33 [dddq, $^2J_{4,4'}$ = 16.1, $^3J_{4',5}$ = 9.1, $^3J_{3,4'}$ = 5.3, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.8 Hz, 1 H, C(4)-H′], 1.67 (quint, ^3J = 6.8 Hz, 2 H, CH_2CH$_2$NFt), 1.54 (quint, ^3J = 7.0 Hz, 2 H, NCH$_2$CH_2), 1.36–1.30 [m, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$NFt or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$-NFt], 1.29 [t, ^3J = 6.9 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.28 [t, ^3J = 6.9 Hz, 3 H, PO(OCH$_2$CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 4.3 Hz, C=O), 168.4 (s, C=O Ft), 133.9 (s, CH Ft), 132.1 (s, Cq Ft), 130.3 [d, $^3J_{3,P}$ = 12.2 Hz, C(3)], 124.2 [d, $^2J_{2,P}$ = 7.8 Hz, C(2)], 123.2 (s, CH Ft), 63.1 [d, ^2J = 6.5 Hz, PO(OCH$_2$CH$_3$)$_2$], 61.9 [d, ^2J = 7.4 Hz, PO(OCH$_2$-CH$_3$)$_2$], 40.7 [d, $^2J_{6,P}$ = 3.3 Hz, C(6)], 38.8 [d, $^3J_{5,P}$ = 7.0 Hz, C(5)], 38.8 (s, NCH$_2$), 37.8 (s, CH$_2$NFt), 34.0 [d, $^1J_{1,P}$ = 146.2 Hz, C(1)], 28.4 [s, NCH$_2$$CH_2$(CH$_2$)$_4$NFt or N(CH$_2$)$_4$$CH_2CH_2$NFt], 27.4 [s, N(CH$_2$)$_4$$CH_2CH_2$NFt or NCH$_2$$CH_2$(CH$_2$)$_4$NFt], 26.4 [s, N(CH$_2$)$_2$-$CH_2$(CH$_2$)$_3$Ft or N(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$NFt], 22.8 [s, C(4)], 16.4 [d, ^3J = 6.3 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.3 [d, ^3J = 6.4 Hz, PO(OCH$_2$-CH$_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.18 ppm. IR: $\tilde{\nu}$ = 2932 (m), 1772 (m, C=O), 1697 (s, C=O), 1436 (m), 1396 (s), 1246 (s, P=O), 1051 (s), 1024 (s, P–O), 962 (s, P–O), 791 (m) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{26}H_{34}N_2O_7P$ (16) [M + H] 517.20981; found 517.20941; calcd. for $C_{26}H_{33}N_2O_7PNa$ (100) [M + Na] 539.19168; found 539.19147; m/z = 1055.39624 (41) [2M + Na].

Preparation of Diethyl (1,1a,3,3a,4,7)-Hexahydro-2-(6-iodohexyl)-2*H*-isoindol-4-phosphonate-1,3-dione (11): In flame-dried flask, **5g** (0.279 g, 0.72 mmol, 1.00 equiv.) was dissolved in anhydrous tetrahydrofuran (4 mL). The polymer-supported triphenylphosphane (3 mmol/g polymer, 0.367 g, 1.53 equiv.), iodine (0.281 g,

1.106 mmol, 1.54 equiv.), and imidazole (98 mg, 1.44 mmol, 2.00 equiv.) were successively added. The mixture was stirred overnight at room temperature. The polymer-supported reagent was removed by filtration and washed with ethyl acetate. Evaporation of the solvent gave a dark residue, which was purified by column chromatography on silica gel (ethyl acetate) to furnish **11** as a brown oil (0.240 g, 67%). R_f = 0.3 (ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.10 [dtt, $^3J_{2,3}$ = 9.4, $^3J_{3,4'}$ = $^4J_{3,5}$ = 4.8, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.4 Hz, 1 H, C(3)-H], 5.99 [dtt, $^3J_{2,3}$ = 9.9, $^3J_{2,P}$ = ^3J = 1 Hz, 1 H or $^4J_{2,6}$ = 5.7 Hz and $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.4 Hz, C(2)-H], 4.22–4.14 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.13–4.07 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 3.47 (m, 2 H, NCH_2), 3.39 [ddd, $^3J_{6,P}$ = 17.7, $^3J_{5,6}$ = 9.2, $^3J_{1,6}$ = 6.5 Hz, 1 H, C(6)-H], 3.18 (t, ^3J = 7.0 Hz, CH_2I), 3.16 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = 4.4 Hz, 1 H, C(5)-H], 3.00 [ddd, $^1J_{1,P}$ = 22.8, $^3J_{1,6}$ = 6.9, $^3J_{1,2}$ = 5.8 Hz, 1 H, C(1)-H], 2.73 [dq, $^2J_{4,4'}$ = 16.5, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 4.0 Hz, 1 H, C(4)-H], 2.39–2.34 [dddq, $^2J_{4,4'}$ = 16.2, $^3J_{4',5}$ = 8.9, $^3J_{3,4'}$ = 5.4, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.8 Hz, 1 H, C(4)-H′], 1.81 (tt, ^3J = 7.3, ^3J = 7.1 Hz, 2 H, NCH$_2$CH_2),1.57 (tt, ^3J = 7.6, ^3J = 7.5 Hz, 2 H, CH_2CH$_2$I),1.41 [tt, ^3J = 7.6, ^3J = 7.4 Hz, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$I or N(CH$_2$)$_3$CH_2(CH$_2$)$_2$I], 1.33 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.30 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.30 [m, 2 H, N(CH$_2$)$_2$CH_2(CH$_2$)$_3$I or N(CH$_2$)$_3$-CH_2(CH$_2$)$_2$I] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0 (s, C=O), 176.7 (d, ^3J = 3.5 Hz, C=O), 130.3 [d, $^3J_{3,P}$ = 12.4 Hz, C(3)], 124.2 [d, $^2J_{2,P}$ = 7.3 Hz, C(2)], 62.9 [d, ^3J = 6.6 Hz, PO(OCH_2-CH$_3$)$_2$], 62.0 [d, ^3J = 6.9 Hz, PO(OCH_2CH$_3$)$_2$], 40.6 [d, $^2J_{6,P}$ = 2.9 Hz, C(6)], 38.9 [d, $^3J_{5,P}$ = 9.3 Hz, C(5)], 38.7 (s, NCH_2), 33.9 [d, $^1J_{1,P}$ = 146.6 Hz, C(1)], 33.2 (s, NCH$_2$$CH_2$), 29.9 [s, N(CH$_2$)$_2$-$CH_2$], 27.3 [s, N(CH$_2$)$_3$$CH_2$(CH$_2$)$_2$I], 25.6 [s, N(CH$_2$)$_4$$CH_2CH_2$I], 22.9 [s, C(4)], 16.3 [d, ^3J = 5.0 Hz, PO(OCH$_2$$CH_3$)$_2$], 16.3 [d, ^3J = 5.4 Hz, PO(OCH$_2$CH_3)$_2$], 6.8 (s, CH_2I) ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 26.06 ppm. IR: $\tilde{\nu}$ = 2989 (m), 2932 (m), 2853 (m), 1737 (s, C=O), 1704 (s, C=O), 1366 (s), 1217 (s, P=O), 1051 (s), 1026 (s, P–O), 962 (s, P–O), 788 (w), 680 (w) cm^{-1}. HRMS (EI): calcd. for $C_{18}H_{29}INO_5P$ (13) [M] 497.08226; found 497.08087; *m/z* = 342 (12) [M – I – CH_2=CH_2], 314 (7) [M – I – 2CH_2=CH_2].

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 12: Sodium hydride (60% dispersion in oil, 29.6 mg, 1.23 mmol, 5 equiv.) was rinsed with a small amount of *n*-hexane (2×) and then suspended in anhydrous tetrahydrofuran (1 mL). To this suspension was added dropwise a solution of diethylphosphite (212.0 µL, 169 mg, 5 equiv.) in anhydrous tetrahydrofuran (212 µL). The evolution of gas (H_2) was observed. The mixture was stirred at room temperature for 30 min (formation of diethyl phosphonate sodium salt). In another flask was dissolved **11** (122.7 mg, 0.25 mmol, 1 equiv.) in anhydrous tetrahydrofuran (1.5 mL). To this solution was added dropwise the solution of the sodium diethylphosphonate salt. The mixture was stirred overnight at 20 °C, and then water (2 mL) was added. The aqueous phase was extracted with ethyl acetate (4×), and the combined organic layers were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (ethyl acetate/acetone, 2:1) to give **12** as yellow oil (68.4 mg, 53%). R_f = 0.4 (ethyl acetate/acetone, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.09–6.02 [m, 1 H, C(3)-H], 5.80–5.73 [m, 1 H, C(2)-H], 4.18–4.11 [m, 4 H, CH$_2$PO(OCH_2CH$_3$)$_2$], 4.07 [q, ^3J = 7.3 Hz, 4 H, CHPO-(OCH_2CH$_3$)$_2$], 3.46 (t, ^3J = 7.2 Hz, 2 H, NCH_2), 3.38 [dd, $^3J_{6,P}$ = 16.3, $^3J_{5,6}$ = 9.3 Hz, 1 H, C(6)-H], 3.30 [dd, $^1J_{1,P}$ = 25.0, $^3J_{1,6}$ = 7.0 Hz, 1 H, C(1)-H], 3.24 [t, $^3J_{5,6}$ = $^3J_{4',5}$ = 8.7 Hz, 1 H, C(5)-H], 2.75 [dtt, $^2J_{4,4'}$ = 17.1, $^3J_{3,4}$ = $^3J_{4,5}$ = 8.8, $^4J_{2,4}$ = $^4J_{4,6}$ = 2.5 Hz, 1 H, C(4)-H], 2.53 [ddt, $^2J_{4,4'}$ = 16.8, $^3J_{3,4'}$ = 6.7, $^4J_{4',6}$ = $^5J_{4',P}$ = 1.7 Hz, 1 H, C(4)-H′], 1.72 [dt, ^2J_P = 17.1, ^3J = 8.5 Hz, 2 H, CH_2PO(OCH$_2$CH$_3$)$_2$], 1.60–1.52 [m, 2 H, NCH$_2$CH_2(CH$_2$)$_4$P or N(CH$_2$)$_4$CH_2CH$_2$P], 1.52 [tt, J = 7.4, J = 7.3 Hz, 2 H, NCH$_2$CH_2(CH$_2$)$_4$P or N(CH$_2$)$_4$CH_2CH$_2$P], 1.40–1.34 [m, 2 H, N(CH$_2$)$_3$CH_2(CH$_2$)$_2$P or N(CH$_2$)$_2$CH_2(CH$_2$)$_3$P], 1.36 [t, ^3J = 7.1 Hz, 6 H, PO(OCH$_2$CH_3)$_2$], 1.31 [t, ^3J = 7.0 Hz, 6 H, CH$_2$PO(OCH$_2$CH_3)$_2$], 1.22 [quint, J = 7.6 Hz, 2 H, N(CH$_2$)$_3$-CH_2(CH$_2$)$_2$P or N(CH$_2$)$_2$CH_2(CH$_2$)$_3$P] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 180.1 (s, C=O), 178.8 (d, ^3J = 18.3 Hz, C=O), 130.7 [d, $^3J_{3,P}$ = 11.2 Hz, C(3)], 121.9 [d, $^2J_{2,P}$ = 9.9 Hz, C(2)], 62.9 [d, ^2J = 6.8 Hz, CHPO(OCH_2CH$_3$)$_2$], 62.6 [d, ^2J = 7.2 Hz, CHPO(OCH_2CH$_3$)$_2$], 61.5 [d, ^2J = 6.4 Hz, CH$_2$PO(OCH_2CH$_3$)$_2$], 39.4 [s, C(6)], 39.3 (s, NCH_2), 38.2 [d, $^3J_{5,P}$ = 2.5 Hz, C(5)], 34.1 [d, $^1J_{1,P}$ = 145.5 Hz, C(1)], 30.1 [d, ^3J = 16.9 Hz, CH_2(CH$_2$)$_2$-PO(OEt)$_2$], 27.4 (s, NCH$_2$$CH_2$), 26.2 [s, N(CH$_2$)$_2$$CH_2$], 25.7 [d, ^1J = 139.4 Hz, CH_2PO(OEt)$_2$], 23.5 [d, $^4J_{4,P}$ = 2.8 Hz, C(4)], 22.4 [d, ^2J = 5.1 Hz, CH_2CH$_2$PO(OEt)$_2$], 16.6 [d, ^3J = 5.6 Hz, CHPO(OCH$_2$$CH_3$)$_2$ and CH$_2$PO(OCH$_2$$CH_3$)$_2$] ppm. ^{31}P NMR (202 MHz, $CDCl_3$): δ = 27.44 [CHPO(OEt)$_2$] and 32.92 [CH$_2$PO(OEt)$_2$] ppm. IR: $\tilde{\nu}$ = 2950 (m), 2916 (m), 1774 (w, C=O), 1697 (s, C=O), 1443 (m), 1404 (m), 1246 (m, P=O), 1049 (s), 1022 (s, P–O), 962 (s, P–O), 792 (w) cm^{-1}. MS (APCI, positive mode): *m/z* (%) = 508.03 (77) [M + H], 480.03 (93) [M + H – CH_2=CH_2], 452.06 (100) [M + H – 2CH_2=CH_2], 424.06 (85) [M + H – 3CH_2=CH_2], 396.08 (80) [M + H – 4CH_2=CH_2]. HRMS (ESI, positive mode): calcd. for $C_{22}H_{40}NO_8P_2$ (100) [M + H] 508.22237; found 508.22183; calcd. for $C_{22}H_{39}NO_8P_2Na$ (37) [M + Na] 530.20431; found 530.20402; calcd. for $C_{44}H_{78}N_2O_{16}P_4Na$ (22) [2M + Na] 1037.41940; found 1037.42044.

General Procedure for Nucleophilic Substitution of Iodide 11: Compound **11** (1 equiv.) was dissolved in anhydrous acetonitrile (2 mL per 0.23 mmol of **11**), and triethylamine (1.2 equiv.) and the nucleophilic amine (1 equiv.) were added successively. The solution was heated at reflux for 12–16 h. After the addition of water, the aqueous phase was extracted with ethyl acetate (4×), and the combined organic layers were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 14: The reaction of **11** (114 mg, 0.229 mmol) with dibenzylamine (44 µL, 45 mg, 0.229 mmol) and triethylamine (26 µL, 278 mg, 0.274 mmol) gave **14** as a yellowish oil (71 mg, 55%). R_f = 0.3 (ethyl acetate). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35 [d, ^3J = 7.3 Hz, 4 H, CH(Ph)], 7.30 [t, ^3J = 7.3 Hz, 4 H, CH(Ph)], 7.22 [t, ^3J = 7.3 Hz, 2 H, CH(Ph)], 6.06 [dtt, $^3J_{2,3}$ = 9.2, $^3J_{3,4'}$ = $^4J_{3,5}$ = 4.6, $^3J_{3,4}$ = $^4J_{3,P}$ = 1.3 Hz, 1 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.1, $^3J_{2,P}$ = $^3J_{1,2}$ = 6.1, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.3 Hz, 1 H, C(2)-H], 4.22–4.12 [m, 2 H, PO(OCH_2CH$_3$)$_2$], 4.07 [q, ^3J = 7.2 Hz, 2 H, PO(OCH_2CH$_3$)$_2$], 3.53 [s, 4 H, N(CH_2Ph)$_2$], 3.41 (m, 2 H, NCH_2), 3.30 [ddd, $^3J_{6,P}$ = 19.3, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.5 Hz, 1 H, C(6)-H], 3.07 [td, $^3J_{5,6}$ = $^3J_{4',5}$ = 9.3, $^3J_{4,5}$ = 4.2 Hz, 1 H, C(5)-H], 2.97 [dt, $^1J_{1,P}$ = 22.8, $^3J_{1,6}$ = $^3J_{1,2}$ = 6.1 Hz, 1 H, C(1)-H], 2.70 [dq, $^2J_{4,4'}$ = 16.6, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 4.0 Hz, 1 H, C(4)-H], 2.38 (t, ^3J = 7.1 Hz, 2 H, CH_2NBn$_2$), 2.34 [dddq, $^2J_{4,4'}$ = 16.4,$^3J_{4',5}$ = 9.2, $^3J_{3,4'}$ = 5.5, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{4',P}$ = 1.8 Hz, C(4)-H′], 1.50 [tt, ^3J = 7.8, ^3J = 7.7 Hz, 2 H, NCH$_2$CH_2(CH$_2$)$_4$-NBn$_2$ or N(CH$_2$)$_4$CH_2CH$_2$NBn$_2$], 1.48 [tt, ^3J = 7.8, ^3J = 7.5 Hz, 2 H, N(CH$_2$)$_4$CH_2CH$_2$NBn$_2$ or NCH$_2$CH_2(CH$_2$)$_4$NBn$_2$], 1.31 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.29 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$CH_3)$_2$], 1.17 [tt, J = 7.6, J = 7.3 Hz, 4 H, N(CH$_2$)$_2$-CH_2(CH$_2$)$_3$NBn$_2$ and N(CH$_2$)$_3$CH_2(CH$_2$)$_2$NBn$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.2 (s, C=O), 176.5 (d, ^3J = 4.3 Hz, C=O), 140.04 [s, Cq(Ph)], 130.4 [d, $^3J_{3,P}$ = 12.2 Hz, C(3)], 128.8 [s, CH(Ph)], 128.2 [s, CH(Ph)], 126.8 [s, CH(Ph)], 124.3 [d, $^2J_{2,P}$ = 7.8 Hz, C(2)], 63.1 [d, ^2J = 6.5 Hz, PO(OCH_2CH$_3$)$_2$], 61.9 [d, ^2J = 7.1 Hz, PO(OCH_2CH$_3$)$_2$], 58.3 [s, N(CH_2Ph)$_2$], 53.2 (s, CH_2NBn$_2$),

40.7 [d, $^2J_{6,P}$ = 3.4 Hz, C(6)], 39.0 (s, N*C*H$_2$), 38.9 [d, $^3J_{5,P}$ = 8.8 Hz, C(5)], 34.1 [d, $^1J_{1,P}$ = 146.2 Hz, C(1)], 27.6 (s, *C*H$_2$CH$_2$NBn$_2$), 26.9 [s, N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$NBn$_2$], 26.9 [s, (CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$NBn$_2$], 26.8 (s, NCH$_2$*C*H$_2$), 22.9 [s, C(4)], 16.5 [d, ^3J = 6.4 Hz, PO(OCH$_2$*C*H$_3$)$_2$], 16.4 [d, ^3J = 7.4 Hz, PO(OCH$_2$*C*H$_3$)$_2$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ = 26.16 ppm. IR: $\tilde{\nu}$ = 2927 (m), 1776 (w, C=O), 1697 (s, C=O), 1494 (m), 1441 (m), 1248 (m, P=O), 1055 (m), 1024 (s, P–O), 960 (s, P–O), 698 (s), 750 (w), 683 (w) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{32}H_{44}N_2O_5P$ (100) [M + H] 567.29824; found 567.29779.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 15: In a flame-dried flask was introduced **11** (114 mg, 0.23 mmol, 1 equiv.) in anhydrous acetonitrile (1.9 mL) in the absence of light. A solution of tetrabutylammonium azide (56.9 mg, 0.229 mmol, 1 equiv.) in anhydrous acetonitrile (0.4 mL) was added dropwise. The mixture was heated at for 45 min (IR control, new band at 2093 cm^{-1} and disappearance of the band at 2004 cm^{-1}). Diethyl ether was poured into the mixture. The insoluble salt (tetrabutylammonium iodide) was removed by filtration, and the solvent was evaporated under reduced pressure to furnish crude **15** as a brown oil (90 mg, 95%). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 6.12–6.02 [m, 1 H, C(3)-H], 6.02–5.92 [m, 1 H, C(2)-H], 4.17 [q, ^3J = 7.1 Hz, 2 H, PO(OC*H*$_2$CH$_3$)$_2$], 4.07 [q, ^3J = 7.1 Hz, 2 H, PO(OC*H*$_2$CH$_3$)$_2$], 3.46 (t, ^3J = 7.2 Hz, 2 H, NC*H*$_2$), 3.33 [ddd, $^3J_{6,P}$ = 18.9, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.4 Hz, 1 H, C(6)-H], 3.25 (t, ^3J = 6.8 Hz, 2 H, C*H*$_2$N$_3$), 3.12 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.3, $^3J_{4,5}$ = 4.2 Hz, 1 H, C(5)-H], 2.98 [dt, $^1J_{1,P}$ = 22.7, $^3J_{1,6}$ = $^3J_{1,2}$ = 6.9 Hz, 1 H, C(1)-H], 2.72 [dq, $^2J_{4,4'}$ = 16.5, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 4.2 Hz, 1 H, C(4)-H], 2.36 [dddq, $^2J_{4,4'}$ = 16.2, $^3J_{4',5}$ = 9.0, $^3J_{3,4'}$ = 5.4, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.8 Hz, 1 H, C(4)-H′], 1.65–1.55 [m, 4 H, NCH$_2$C*H*$_2$(CH$_2$)$_4$N$_3$ and N(CH$_2$)$_4$C*H*$_2$CH$_2$N$_3$], 1.50–1.35 [m, 4 H, N(CH$_2$)$_2$C*H*$_2$(CH$_2$)$_3$N$_3$ and N(CH$_2$)$_3$C*H*$_2$(CH$_2$)$_2$N$_3$], 1.31 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$C*H*$_3$)$_2$], 1.30 [t, ^3J = 7.0 Hz, 3 H, PO(OCH$_2$C*H*$_3$)$_2$] ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 179.2 (s, C=O), 176.6 (d, ^3J = 4.6 Hz, C=O), 130.4 [d, $^3J_{3,P}$ = 13.0 Hz, C(3)], 124.3 [d, $^2J_{2,P}$ = 7.8 Hz, C(2)], 63.1 [d, ^3J = 6.8 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 62.0 [d, ^3J = 7.1 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 51.4 (s, *C*H$_2$N$_3$), 40.7 [d, $^2J_{6,P}$ = 3.4 Hz, C(6)], 38.9 [d, $^3J_{5,P}$ = 9.3 Hz, C(5)], 38.9 (s, N*C*H$_2$), 34.1 [d, $^1J_{1,P}$ = 146.3 Hz, C(1)], 28.7 (s, NCH$_2$*C*H$_2$), 27.5 (s, *C*H$_2$CH$_2$N$_3$), 26.4 [s, N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$N$_3$ or N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$N$_3$], 26.3 [s, N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$N$_3$ or N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$N$_3$], 22.9 [s, C(4)], 16.5 [d, ^3J = 4.6 Hz, PO(OCH$_2$*C*H$_3$)$_2$], 16.4 [d, ^3J = 5.5 Hz, PO(OCH$_2$*C*H$_3$)$_2$] ppm. ^{31}P NMR (121 MHz, CDCl$_3$): δ = 26.08 ppm.

1,3-Dioxo-hexahydro-1*H*-isoindole Derivative 17: Compound **15** (201 mg, 0.487 mmol, 1 equiv.) was dissolved in a solution of *t*BuOH/H$_2$O (1:1; total volume of 5.4 mL). Phenylacetylene (54 μL, 49.8 mg, 0.487 mmol, 1 equiv.), pentahydrate copper sulfate (49 mg, 0.194 mmol, 0.4 equiv.), and sodium ascorbate (78 mg, 0.394 mmol, 0.8 equiv.) were successively added. The reaction mixture was stirred at room temperature overnight. After the addition of water, the aqueous phase was extracted with ethyl acetate (4×), and the combined organic layers were dried with magnesium sulfate. The solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (acetonitrile) to give **17** as a colorless oil (116.8 mg, 46%). R_f = 0.3 (acetonitrile). ^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.83 [d, ^3J = 8.0 Hz, 2 H, CH(Ph)], 7.82 [s, 1 H, CH(triazole)], 7.41 [t, ^3J = 7.8 Hz, 2 H, CH(Ph)], 7.34–7.30 [m, 1 H, CH(Ph)], 6.11–6.05 [m, 1 H, C(3)-H], 5.98 [dtt, $^3J_{2,3}$ = 9.1, $^3J_{2,P}$ = $^3J_{1,2}$ = 5.8, $^4J_{2,4'}$ = $^4J_{2,4}$ = 1.6 Hz, 1 H, C(2)-H], 4.36 (t, ^3J = 7.1 Hz, 2 H, C*H*$_2$triazole), 4.20–4.15 [m, 4 H, PO(OC*H*$_2$CH$_3$)$_2$], 3.48–3.40 (m, 2 H, NC*H*$_2$), 3.31 [ddd, $^3J_{6,P}$ = 18.8, $^3J_{5,6}$ = 9.4, $^3J_{1,6}$ = 6.8 Hz, 1 H, C(6)-H], 3.10 [td, $^3J_{4',5}$ = $^3J_{5,6}$ = 9.2, $^3J_{4,5}$ = 4.5 Hz, 1 H, C(5)-H], 2.96 [dt, $^1J_{1,P}$ = 22.8, $^3J_{1,6}$ = $^3J_{1,2}$ = 6.7 Hz, 1 H, C(1)-H], 2.70 [dq, $^2J_{4,4'}$ = 16.4, $^3J_{4,5}$ = $^5J_{4,P}$ = $^3J_{3,4}$ = 2.4 Hz, 1 H, C(4)-H], 2.34 [dddq, $^2J_{4,4'}$ = 16.4, $^3J_{4',5}$ = 9.1, $^3J_{3,4'}$ = 5.7, $^4J_{2,4'}$ = $^4J_{4',6}$ = $^5J_{1,4'}$ = 1.7 Hz, 1 H, C(4)-H′], 1.92 (tt, ^3J = 6.7, ^3J = 6.6 Hz, 2 H, C*H*$_2$CH$_2$triazole), 1.55 (tt, ^3J = 6.4, ^3J = 6.1 Hz, 2 H, NCH$_2$C*H*$_2$),1.38–1.32 [m, 4 H, N(CH$_2$)$_2$-C*H*$_2$(CH$_2$)$_3$N and N(CH$_2$)$_3$C*H*$_2$(CH$_2$)$_2$N], 1.29 [t, ^3J = 7.0 Hz, 6 H, PO(OCH$_2$C*H*$_3$)$_2$] ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 179.1 (s, C=O), 176.4 (d, ^3J = 4.4 Hz, C=O), 147.5 [s, Cq(triazole)], 130.6 [s, Cq(Ph)], 130.2 [d, $^3J_{3,P}$ = 12.3 Hz, C(3)], 128.7 [s, CH(Ph)], 127.9 [s, CH(Ph)], 125.5 [s, CH(Ph)], 124.1 [d, $^2J_{2,P}$ = 7.7 Hz, C(2)], 119.6 [s, CH(triazole)], 62.8 [d, ^3J = 6.6 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 61.8 [d, ^3J = 7.0 Hz, PO(O*C*H$_2$CH$_3$)$_2$], 50.1 (s, *C*H$_2$Ntriazole), 40.5 [d, $^2J_{6,P}$ = 3.1 Hz, C(6)], 38.7 [d, $^3J_{5,P}$ = 8.9 Hz, C(5)], 38.5 (s, NCH$_2$), 33.8 [d, $^1J_{1,P}$ = 146.1 Hz, C(1)], 30.0 (s, NCH$_2$*C*H$_2$), 27.1 (s, *C*H$_2$CH$_2$triazole), 26.0 [s, N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$N or N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$N], 25.8 [s, N(CH$_2$)$_3$*C*H$_2$(CH$_2$)$_2$N or N(CH$_2$)$_2$*C*H$_2$(CH$_2$)$_3$N], 22.7 [s, C(4)], 16.3 [d, ^3J = 6.5 Hz, PO(OCH$_2$*C*H$_3$)$_2$], 16.2 [d, ^3J = 6.8 Hz, PO(OCH$_2$*C*H$_3$)$_2$] ppm. ^{31}P NMR (202 MHz, CDCl$_3$): δ = 26.05 ppm. IR: $\tilde{\nu}$ = 2935 (m), 1776 (m, C=O), 1697 (s, C=O), 1439 (m), 1402 (s), 1248 (m, P=O), 1022 (s, P–O), 960 (s, P–O), 768 (s), 696 (s) cm^{-1}. HRMS (ESI, positive mode): calcd. for $C_{26}H_{35}O_5N_4P$ (100) [M + H] 515.24178; found 515.21124.

2. Complexation Studies

2.1 ESI-HRMS: ESI-HRMS analyses (for coordination and competition experiments) were performed with a LTQ-Orbitrap XL hybrid mass spectrometer (Thermo Fisher Scientific, Bremen, Germany). Data were acquired in the positive ion mode, using a full-scan MS with a mass range of 200–2000 *m*/*z*. The orbitrap operated at 30,000 resolution [FWHM (full width at half maximum) definition]. All experimental data were acquired, along with a daily external calibration prior to the data acquisition. The appropriate tuning of the electrospray ion source was done to ensure the preservation of the complexes formed in the solution, but to avoid the detection of adducts formed during the ESI process. The following electrospray inlet conditions were applied: flow rate, 200 μL min^{-1}; spray voltage, 5 kV; sheath gas (N$_2$) flow rate, 20 a.u.; auxiliary gas (N$_2$) flow rate, 20 a.u.; capillary temperature, 275 °C; capillary voltage, 45 V; and tube lens, 80 V. The salts, which were purchased from Aldrich, Alpha, or Acros, were of the highest quality available and vacuum dried at room temperature over P_2O_5 prior to use. Acetonitrile from Biolsolve (LC–MS grade) and ethanol from Fisher (absolute) were used for the MS experiments. For all experiments, the concentration of the ligand was approximately 0.5 mM with 5 equiv. of cation. For the fragmentation experiments, the fragmentation in the source was also tested between 0 and 100 (maximum value) relative units to check the stability of the complexes. For the competition experiments between two ligands and one metallic cation, the concentration of each ligand was 0.25 mM with 5 equiv. of cation. For the competition experiments between one ligand and two cations, the concentration of the ligand was 0.5 mM with 2.5 equiv. of each cation.

2.2 Photoluminescence: Eu(NO$_3$)$_3$·5H$_2$O (99.9%) was purchased from Aldrich, and the acetonitrile for the analysis was used without further purification. The luminescent measurements were recorded with a Varian Cary Eclipse spectrophotometer. The emission spectra were measured in 1 cm path-length quartz cells in photo counts and corrected for the instrumental function. Ligand **12** (0.113 M solution in acetonitrile) was titrated with Eu(NO$_3$)$_3$·5H$_2$O (5.999×10^{-3} M solution in acetonitrile). The emission spectra were recorded in the Eu^{III} photoluminescence region (550–675 nm). The spectrophotometer parameters were held constant during the entire time of the titration [excitation at 244.67 nm (Ligand); PMT volt-

age, 600 V; slits, 10/10; and scans, medium]. The intensity of ($^5D_0 \rightarrow {}^7F_2$) the major Eu^{III} emission band of each emission spectra was determined with a lorentzien simulation using Microcal™ Origin® 6.0 software (© 1991–1999 Microcal software, Inc.). These intensities were corrected by a dilution factor (equal to total volume/initial volume) and reported as a function of the ratio [Eu^{III}]/[**12**] to obtain the titration curve.

Supporting Information (see footnote on the first page of this article): Procedures used for the preparation of maleimides **3a**–**3j**, cycloadduct **5f**, and functionalized cycloadducts **8**, **9′**, and **13**; all NMR spectra of maleimides **3b**–**3e** and **3j**, cycloadducts **5a**–**5j**, and products **6**–**15** and **17**; representative ESI-HRMS spectra, tables of exact masses, and titration data are recorded in the Supporting Information

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[1] a) P. Savignac, B. Iorga, *Modern Phosphonate Chemistry*, CRC Press LLC, Boca Raton, **2003**; b) V. P. Kukkhar, H. R. Hudson, *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Applications*, John Wiley & Sons Ltd., Chichester, UK, **2000**.

[2] a) A. Clearfield, K. D. Demadis (Eds.), *Metal Phosphonate Chemistry: From Synthesis to Applications*, RSC Publishing, Cambridge, UK, **2012**; b) C. Maillet, P. Janvier, M.-J. Bertrand, T. Praveen, B. Bujoli, *Hybrid Organic Inorganic Materials Based on Organophosphorus Derivatives*, Springer, Berlin/Heidelberg, **2004**.

[3] a) G. Guerrero, P. H. Mutin, A. Viaux, *Chem. Mater.* **2001**, *13*, 4367–4373; b) P. Péchy, F. P. Rotzinger, M. K. Nazeeruddin, O. Kohle, S. M. Zakeeruddin, R. Humphry-Baker, M. Grätzel, *J. Chem. Soc., Chem. Commun.* **1995**, 65–66.

[4] a) F. Corbellini, W. B. F. van Leeuwen, H. Beiljleveld, H. Kooijman, A. L. Spek, W. Verboom, M. Crego-Calama, D. Reinhoudt, *New J. Chem.* **2005**, *29*, 243–248; b) A.-S. Chauvin, S. Comby, M. Baud, C. De Piano, C. Duhot, J.-C. G. Bünzli, *Inorg. Chem.* **2009**, *48*, 10687–10696.

[5] a) E. V. Bakhmutova, X. Ouyang, D. G. Medvedev, A. Clearfield, *Inorg. Chem.* **2003**, *42*, 7046–7051; b) J. G. Van Alsten, *Langmuir* **1999**, *15*, 7605–7614; c) H. C. Yang, K. Aoki, H. G. Hong, D. D. Sackett, M. F. Arendt, S. L. Yau, C. M. Bell, T. E. Mallouk, *J. Am. Chem. Soc.* **1993**, *115*, 11855–11862; d) H. G. Hong, D. D. Sackett, T. E. Mallouk, *Chem. Mater.* **1991**, *3*, 521–527.

[6] a) C. M. Mikulski, W. Henry, L. L. Pytlewski, N. M. Karayannis, *Transition Met. Chem.* **1997**, *2*, 135–140; b) G. Pawlicki, S. Lis, *Opt. Mater.* **2011**, *33*, 1544–1547.

[7] A. M. J. Lees, R. A. Kresinski, A. W. G. Platt, *New J. Chem.* **2004**, *28*, 1457–1463.

[8] a) E. Villemin, B. Elias, R. Robiette, M.-F. Herent, J.-L. Habib-Jiwan, J. Marchand-Brynaert, *Tetrahedron Lett.* **2011**, *52*, 5140–5144; b) J.-C. Monbaliu, E. Villemin, B. Elias, J. Marchand-Brynaert, in: *Targets in Heterocyclic Systems* (Eds: O. A. Attonasi, D. Spinelli), RSC Publishing, Cambridge, **2010**, vol. 14, pp. 49–79.

[9] a) R. Marcia de Figueiredo, P. Oczipka, R. Fröhlich, M. Christmann, *Synthesis* **2008**, *8*, 1316–1318; b) L. Peng, G. Zhang, D. Zhang, J. Xiang, R. Zhao, Y. Wang, D. Zhu, *Org. Lett.* **2009**, *11*, 4014–4017.

[10] a) K. A. Keller, J. Guo, S. Panna, M. G. Finn, *Tetrahedron Lett.* **2005**, *46*, 1181–1184; b) C. Sun, S. E. Aspland, C. Ballatore, R. Castillo, A. B. Smith, A. J. Castellino, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 104–107; c) O. Keller, J. Rudinger, *Helv. Chim. Acta* **1975**, *58*, 531–541.

[11] A. L. Schwartz, L. M. Lerner, *J. Org. Chem.* **1974**, *39*, 21–23.

[12] a) H. Dalton King, G. M. Dubowchik, M. A. Walker, *Tetrahedron Lett.* **2002**, *43*, 1987–1990; b) T. R. Hoye, V. Dvornikovs, E. Sizova, *Org. Lett.* **2006**, *8*, 5091–5194.

[13] R. C. Clevenger, K. D. Turnbull, *Synth. Commun.* **2000**, *30*, 1379–1398.

[14] a) X. Chen, M. A. Dam, K. Ono, A. Mal, H. Shen, S. R. Nutt, K. Sheran, F. Wudl, *Science* **2002**, *295*, 1698–1702; b) K. Adachi, A. K. Achimuthu, Y. Chujo, *Macromolecules* **2004**, *37*, 9793–9797; c) J. R. McElhanon, D. R. Wheeler, *Org. Lett.* **2001**, *3*, 2681–2683; d) G. J. Gabriel, J. A. Maegerlein, C. F. Nelson, J. M. Dabkowski, T. Eren, K. Nüsslein, G. N. Tew, *Chem. Eur. J.* **2009**, *15*, 433–439; e) W. H. Binder, C. Kluger, *Macromolecules* **2004**, *37*, 9321–9330; f) J. Zhu, A. J. Kell, M. S. Workentin, *Org. Lett.* **2006**, *8*, 4993–4996; g) A. B. Samsam Bakhtiari, D. Hsiao, G. Jin, B. D. Gates, N. R. Branda, *Angew. Chem.* **2009**, *121*, 4230; *Angew. Chem. Int. Ed.* **2009**, *48*, 4166–4169; h) X. Liu, M. Zhu, S. Chen, M. Yuan, Y. Guo, Y. Song, H. Liu, Y. Li, *Langmuir* **2008**, *24*, 11967–11974.

[15] M. Kwart, I. Burchuk, *J. Am. Chem. Soc.* **1952**, *74*, 3094–3097.

[16] J. C. Cheronis, E. T. Whalley, K. T. Nguyen, S. R. Eubanks, L. G. Allen, M. J. Duggan, S. D. Loy, K. A. Bonham, J. K. Blodgett, *J. Med. Chem.* **1992**, *35*, 1563–1572.

[17] J.-C. Monbaliu, J. Marchand-Brynaert, *Synthesis* **2009**, *11*, 1876–1880.

[18] C. E. Griffin, W. M. Daniewski, *J. Org. Chem.* **1970**, *35*, 1691–1693.

[19] J. Beck, L. Maton, J.-L. Habib Jiwan, J. Marchand-Brynaert, *Amino Acids* **2011**, *40*, 679–689.

[20] G. Vicentini, L. B. Zinner, J. Zukerman-Schpector, K. Zinner, *Coord. Chem. Rev.* **2000**, *196*, 353–382.

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Phosphonated Ligands

Phosphonated molecules, featuring a half-cage structure were prepared by a Diels–Alder reaction of 1-diethoxyphosphoryl-1,3-butadiene with a series of maleimides. Postfunctionalization of the cycloadducts allowed the introduction of various functional groups (FG). Metal chelating properties of these molecules were demonstrated in solution using ESI-HRMS and photoluminescence spectroscopy.

Keywords: P ligands / Chelates / Cycloaddition / Luminescence

