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Lanthanide-Catalyzed Selective Addition of Diethyl Phosphite to Chalcones

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ABSTRACT: *Lanthanide-catalyzed addition of diethyl phosphite with chalcones was achieved under mild conditions. The reaction exhibited good product selectivity using different catalysts. γ-Oxophosphonates were obtained in high yields in the reactions catalyzed by $Yb(OAr)_3(THF)_2$, while those catalyzed by $[(Me_3Si)_2N]_3La(\mu\text{-}Cl)Li(THF)_3$ afforded 1,2-oxaphospholane-5-phosphonates as the main products in moderate to good yields. This methodology provides facile and practical approaches to the corresponding organophosphorus compounds with biological interest.* © 2013 Wiley Periodicals, Inc. Heteroatom Chem. 24:345–354, 2013; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.21099

INTRODUCTION

The richness and diversity of organophosphorus compounds have made organophosphorus chemistry [1] a subject of intense research over the last few decades. Accompanied by the increasing use of organophosphorus compounds in many different fields, including medicine, agriculture, organic optoelectronics, and homogeneous catalysis [2–9], much attention has been focused on efficient strategies to construct carbon–phosphorus bonds [10]. Among the various routes reported, cross coupling of phosphorus agents with aryl halides or triflates [11–15] and addition of phosphorus-based nucleophiles (P-nucleophiles) to activated carbon atoms are the most direct and efficient routes to form carbon–phosphorus bonds. The latter, which includes the well-known Pudovik reaction [16–25] and phospha-Michael addition [26], is a more concise route that maximizes atom efficiency and results in negligible waste.

Phospha-Michael addition, which is the conjugated addition of P-nucleophiles to activated alkenes, is important in carbon–phosphorus bond formation and its catalysts, scope, and applications have been explored. Phosphine [27–32], trialkyl phosphite [33–41], and dialkyl phosphite are commonly used P-nucleophiles in these addition reactions. Considering the stability and smell of phosphorus reagents, dialkyl phosphite is the preferred choice and is also readily available. Phospha-Michael addition also requires an olefinic acceptor, which is typically an α,β-unsaturated ketone [42–46], ester [45–48], nitrile, or nitroalkene [49–53]. Unlike the other reactions, those involving α,β-unsaturated ketones remain a challenge in terms of substrate scope and product selectivity. For example, the vast majority of the α,β-unsaturated ketones, used previously in phospha-Michael addition, was limited to several specific compounds such as methylvinylketone and cyclic enones, and the steric hindrance was the only factor discussed in detail affecting the product regioselectivity. Recently, Wang and coworkers

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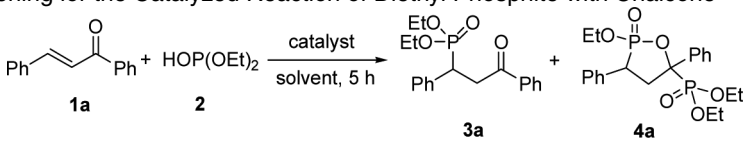
TABLE 1 Condition Screening for the Catalyzed Reaction of Diethyl Phosphite with Chalcone[a]



						Yield (%)[b]	
Entry	*Catalyst*	*Loading (mol%)*	*Solvent*	*T (°C)*	***1a:2***	***3a***	***4a***
1	$Yb(OAr^1)_3(THF)_2$[c]	2.5	THF	25	1:1.2	21[d]	nd[e]
2	$Yb(OAr^1)_3(THF)_2$[c]	5	THF	25	1:1.2	92(94[d])	nd[e]
3	$Nd(OAr^1)_3(THF)_2$[c]	5	THF	25	1:1.2	70	nd[e]
4	$La(OAr^1)_3(THF)_2$[c]	5	THF	25	1:1.2	67	nd[e]
5	$Yb(OAr^2)_3(THF)_2$[f]	5	THF	25	1:1.2	84	nd[e]
6	$Yb(OAr^3)_3(THF)_2$[g]	5	THF	25	1:1.2	81	nd[e]
7	$La(OAr^1)_3(THF)_2$[c]	5	THF	25	1:3	47	nd[e]
8	$Yb(OTf)_3$	20	THF	25	1:1.2	nd	nd[e]
9	$NaOAr^1$[c]	15	THF	25	1:1.2	59	trace
10	$[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$	1	THF	18	1:1.2	58	nd[e]
11	$[(Me_3Si)_2N]_3Yb(\mu\text{-Cl})Li(THF)_3$	2	toluene	18	1:1.2	85	nd[e]
12	$[(Me_3Si)_2N]_3Sm(\mu\text{-Cl})Li(THF)_3$	2	toluene	18	1:1.2	67	15
13	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	2	toluene	18	1:1.2	54	30
14	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	2	toluene	40	1:3	41	52
15	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	2	T/H[h]	40	1:3	13	71
16	$[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$	4	T/H[h]	40	1:3	18	80
17	$Li[N(TMS)_2]$	12	T/H[h]	40	1:3	30	15

[a]Reactions were performed with 1 mmol chalcone **1a** in 2 mL of solvent for 5 h.
[b]Isolated yield.
[c]$Ar^1 = 2,6\text{-}(^t\text{Bu})_2\text{–}4\text{-Me}C_6H_2$.
[d]HPLC yield.
[e]Not detected.
[f]$Ar^2 = 2,6\text{-}(^i\text{Pr})_2C_6H_3$.
[g]$Ar^3 = 2,6\text{-}Me_2C_6H_3$.
[h]Toluene:HMPA = 5:1.

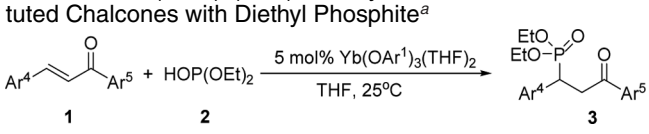
reacted diethyl phosphite with chalcones in the presence of 40 mol% Et_2Zn to form γ-oxophosphonates in high yields with excellent enantioselectivities [54]. This is the only example of phospha-Michael addition using dialkyl phosphite as a nucleophile and chalcone as an olefinic acceptor to synthesize biologically active γ-oxophosphonates [55–57].

During our recent investigation of lanthanide-catalyzed Pudovik reactions, we found that lanthanide amides were highly efficient catalysts for the hydrophosphonylation of aromatic aldehydes to form α-hydroxy phosphonates [24]. However, lanthanide complexes have not yet been used as catalysts in phospha-Michael addition. Here, we report preliminary results showing that lanthanide aryloxides $Ln(OAr)_3(THF)_2$ and lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ show high catalytic activity in the phospha-Michael addition of diethyl phosphite and chalcones. Moreover, these lanthanide catalysts show unprecedented product selectivity: γ-oxophosphonates were afforded in high yields with $Ln(OAr)_3(THF)_2$ as the catalyst, whereas 1,2-oxaphospholane-5-phosphonates were obtained as major products using $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$. Although lanthanide-catalyzed enantioselective reactions have been well studied, less attention was paid to the catalyst-controlled product-selective reactions involving lanthanide complexes and successful examples were rather limited.

RESULTS AND DISCUSSION

We first investigated the catalytic activity of $Yb(OAr^1)_3(THF)_2$ [$Ar^1 = 2,6\text{-}(^t\text{Bu})_2\text{–}4\text{-Me}C_6H_2$] for the reaction using chalcone **1a** and diethyl phosphite as model substrates (Table 1). Diethyl (3-oxo-1,3-diphenylpropyl)phosphonate **3a**, the 1,4-adduct from this reaction, was obtained in 21% yield when 2.5 mol% of $Yb(OAr^1)_3(THF)_2$ was used (Table 1, entry 1). When the catalyst loading was increased to 5 mol%, the reaction proceeded effectively and the yield increased dramatically to 94% (Table 1, entry 2). To reveal the reason for the activity of $Yb(OAr^1)_3(THF)_2$, $Yb(OTf)_3$ and $NaOAr^1$ were also used as catalysts. The reaction did not proceed with $Yb(OTf)_3$ (Table 1, entry 8), which is a strong Lewis acid, while $NaOAr^1$ (15 mol%) gave the corresponding γ-oxophosphonate in 59% yield (Table 1, entry

TABLE 2 $Yb(OAr^1)_3(THF)_2$-Catalyzed Reactions of Substituted Chalcones with Diethyl Phosphite[a]



1 2 3

Entry	Ar^4	Ar^5	Product	Yield (%)[b]
1	Ph	Ph	**3a**	92
2	2-$CH_3C_6H_4$	Ph	**3b**	92
3	2-$CH_3OC_6H_4$	Ph	**3c**	87
4	4-$CH_3C_6H_4$	Ph	**3d**	93
5	4-$CH_3OC_6H_4$	Ph	**3e**	89
6	4-ClC_6H_4	Ph	**3f**	90
7	4-BrC_6H_4	Ph	**3g**	92
8	1-naphthyl	Ph	**3h**	86
9	Ph	4-$CH_3C_6H_4$	**3i**	86
10	Ph	4-$CH_3OC_6H_4$	**3j**	80
11	Ph	4-ClC_6H_4	**3k**	96
12	Ph	4-BrC_6H_4	**3l**	95
13	4-ClC_6H_4	4-ClC_6H_4	**3m**	85

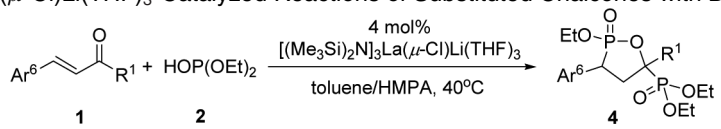
[a]Reactions were performed with 1 mmol chalcone and 1.2 mmol diethyl phosphite in 2 mL of THF for 5 h. $Ar^1 = 2,6\text{-}(^t Bu)_2\text{–}4\text{-}MeC_6H_2$.
[b]Isolated yield.

9), indicating that the activity of $Yb(OAr^1)_3(THF)_2$ may result from the cooperation of lanthanide cation and aryloxide anion. Several different lanthanides were then investigated to examine the effect of the cation on catalytic activity (Table 1, entries 2–4). The aryloxide complex of Yb, the lanthanide with the smallest ionic radius and strongest Lewis acidity of those tested, gave the best result. According to our previous work [58], the steric hindrance of the aryloxide ligand has a large influence on the reactivity of $Ln(OAr)_3(THF)_2$. Therefore, we tested $Yb(OAr)_3(THF)_2$ with different Ar groups. The results showed that the more bulky Ar, the higher the catalytic activity of $Ln(OAr)_3(THF)_2$ (Table 1, entries 2,5, and 6). This conclusion is consistent with that obtained previously and it may be because the elongated Ln–O bond distance caused by the more bulky aryloxide ligand increases the Lewis acidity of the Ln cation.

Considering the above results, we decided to use $Yb(OAr^1)_3(THF)_2$ as the catalyst in the reactions of various substituted chalcones and diethyl phosphite. Table 2 shows that all the substrates examined in this study underwent phospha-Michael addition smoothly, with effective conversion occurring within 5 h in the presence of 5 mol% catalyst at room temperature, to afford the corresponding γ-oxophosphonates in high yields. The reaction was general for chalcones with the phenyl ring at 3-position bearing substituents at ortho- and para-positions, regardless of their electronic nature. The reactivity of chalcones with the phenyl group at 1-position bearing electron-withdrawing groups was somewhat higher than that of those bearing electron-donating groups.

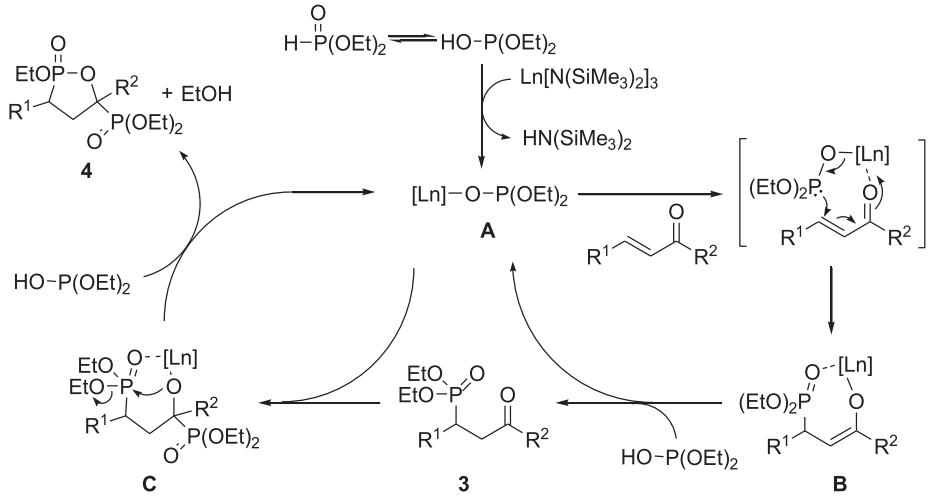
Tetracoordinate lanthanide amides $[(Me_3Si)_2N]_3Ln(\mu\text{-}Cl)Li(THF)_3$ [59–63], which are the chloride-bridged "ate" complexes derived from $Ln[N(SiMe_3)_2]_3$ but more readily available than the latter, are efficient catalysts for several useful transformations such as aldol condensation [64], polymerization of methyl methacrylate [61, 62], aza-Henry reaction [65], guanylation of amines [66], Pudovik reaction [24], and phospha-Brook rearrangement [67]. During the catalyst screening, we found that $[(Me_3Si)_2N]_3Yb(\mu\text{-}Cl)Li(THF)_3$ also works well as a catalyst for the above phospha-Michael addition to afford γ-oxophosphonate **3a** in good yield (Table 1, entry 10). We then optimized the central metal of this catalyst. Increasing the ionic radius of Ln(III) from the heavy rare earth Yb to light rare earth La led to a progressive decrease in the yield of **3a**. Conversely, a gradual increase in the yield of diethyl (2-ethoxy-2-oxido-3,5-diphenyl-1,2-oxaphospholan-5-yl)phosphonate **4a**, another product that can be formed via sequential phospha-Michael/Pudovik reaction of chalcone with diethyl phosphite, was observed (Table 1, entries 11–13). To our knowledge, 2-oxido-1,2-oxaphospholanes displays potential biological activity [68–76]. The preparation of these P(V)-heterocyclic molecules has already attracted considerable attention [77–83], but complex and inaccessible substrates were used in most approaches. Limited literature described the synthesis of (2-oxido-1,2-oxaphospholan-5-yl)phosphonates, which can be used as flame retardants in epoxy resins, via the reaction of dialkyl phosphites with vinyl ketones or aldehydes in the presence of sodium and the yields were not satisfactory [84–86]. Therefore, we conceived the idea of developing efficient and practical methods for the synthesis of 2-oxido-1,2-oxaphospholanes under mild conditions. Further screening of conditions revealed that increasing the reaction temperature and the quantity of diethyl phosphite made 1,2-oxaphospholane a main product (Table 1, entry 14). Notably, when $La(OAr^1)_3(THF)_2$ was used as the catalyst, **4a** was not detected even upon the addition of three equivalents of diethyl phosphite (Table 1, entry 7). Using a mixed solvent of toluene and hexamethylphosphoramide (HMPA, volume ratio 5:1) considerably improved the yield of **4a** (Table 1, entry 15). When the catalyst loading was increased to 4 mol%, the catalytic performance was further enhanced (Table 1, entry 16). The control reaction using $Li[N(TMS)_2]$ (12 mol%) as a catalyst gave γ-oxophosphonate and 1,2-oxaphospholane in

TABLE 3 $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$-Catalyzed Reactions of Substituted Chalcones with Diethyl Phosphite[a]



Entry	*Ar^6*	*R^1*	*Time (h)*	*Product*	*Yield (%)[b]*	*Ratio of Isomers (major : minor)[c]*
1	Ph	Ph	5	**4a**	80	1.1:1
2	4-ClC_6H_4	Ph	5	**4b**	86	1.3:1
3	4-BrC_6H_4	Ph	5	**4c**	80	2.5:1
4	4-$CH_3C_6H_4$	Ph	5	**4d**	58	1.8:1
5	4-$CH_3OC_6H_4$	Ph	5	**4e**	66	1.4:1
6	4-$(CH_3)_2NC_6H_4$	Ph	5	**4f**	60	2.4:1
7	2-$CH_3C_6H_4$	Ph	10	**4g**	53	8.4:1
8	1-naphthyl	Ph	12	**4h**	35	8.3:1
9	Ph	4-$CH_3OC_6H_4$	10	**4i**	61	1.0:1
10	Ph	4-ClC_6H_4	10	**4j**	65	3.1:1
11	Ph	4-BrC_6H_4	10	**4k**	61	1.6:1
12	4-ClC_6H_4	4-ClC_6H_4	5	**4l**	71	1.9:1
13	Ph	Me	5	**4m**	79	4.1:1

[a]Reactions were performed with 1 mmol chalcone and 3 mmol diethyl phosphite in 2 mL of solvent (toluene/HMPA = 5/1).
[b]Isolated yields.
[c]Determined by ^{31}P NMR spectroscopy.

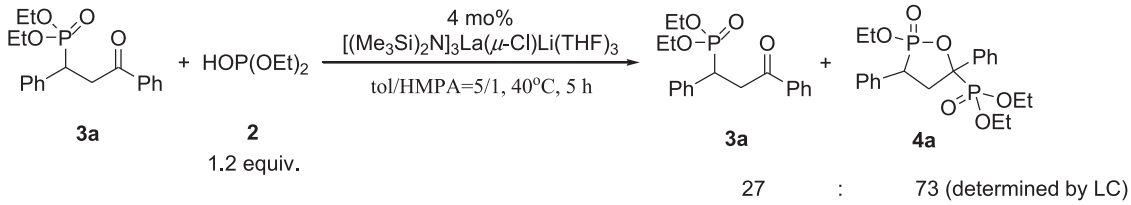


SCHEME 1 Proposed mechanism for the lanthanide-catalyzed addition of diethyl phosphite to chalcone.

yields of 30% and 15%, respectively (Table 1, entry 17), indicating the importance of the lanthanide ion in the catalyst.

To demonstrate the generality of this route to 1,2-oxaphospholane, the process was extended to a serial of substituted chalcones using $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ as a representative lanthanide catalyst. The corresponding 1,2-oxaphospholane-5-phosphonates were obtained in moderate to high yields, as summarized in Table 3. When the aryl at 3-position of chalcone was 1-naphthyl or 2-methylphenyl, relatively lower yields were obtained even after a prolonged reaction time (Table 1, entries 7 and 8), indicating obvious steric effects. An electronic effect was also observed: the activity of chalcones with the aryl at 3-position bearing electron-withdrawing groups was higher than that of those bearing electron-donating groups. 4-Phenylbut-3-en-2-one reacted similarly to chalcones (Table 1, entry 13). The ^{31}P nuclear magnetic resonance (NMR) spectra indicated that the reaction affords the product as a mixture of cis and trans isomers. However, unambiguous assignment of each diastereomer had no success.

According to the distinctive properties of $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$, the proposed mechanism (Scheme 1) for this reaction may involve rapid deprotonation of diethyl phosphite to release amine and form intermediate **A**, which is probably the catalytically active species. The coordination of the lan-



SCHEME 2 Transformation of **3a** into **4a**.

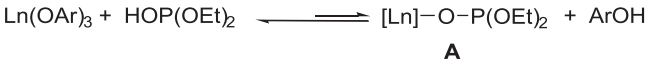
thanide center in species **A** with the carbonyl group may both activate the chalcone and lead to a close contact between the enone and P-nucleophile. Intermediate **B** is then formed by phospha-Michael addition, followed by proton exchange with another phosphite to release γ-oxophosphonate **3** and regenerate **A**. **A** then undergoes a Pudovik reaction with **3** to form intermediate **C**, which subsequently cyclizes by intramolecular ester exchange to give 1,2-oxaphospholane-5-phosphonate **4** and regenerate **A**. The analyses of the crude products of the reaction with **3a** as a substrate (Scheme 2) indicated that most of **3a** is transformed into **4a**, verifying that **3a** is the intermediate during the formation of **4a**. When $Ln(OAr)_3(THF)_2$ is used as a catalyst, the deprotonation equilibrium of diethyl phosphite may be reversed because of the relatively strong acidity of ArOH (Scheme 3). The concentration of **A** in the reaction mixture may be low and the phosphorus-nucleophilic attack is hindered. Finally, the second catalytic cycle involving the relatively difficult Pudovik reaction of steric bulky ketone may be inhibited.

In conclusion, efficient phospha-Michael addition of diethyl phosphite with chalcones was achieved in the presence of catalytic amounts of lanthanide complexes under mild conditions. The reaction exhibited good product selectivity using different catalysts. γ-Oxophosphonates could be obtained in high yields in the reactions catalyzed by $Yb(OAr^1)_3(THF)_2$ [Ar^1 = 2,6-(^{t}Bu)$_2$–4-MeC_6H_2], whereas those catalyzed by $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ afforded 1,2-oxaphospholane-5-phosphonates as the major products in moderate to good yields. This catalyst-controlled product selectivity induced by lanthanide complexes provided facile and practical approaches to produce the corresponding organophosphorus compounds with biological interest.

EXPERIMENTAL

General Remarks

All operations involving air- and moisture-sensitive compounds were carried out under an inert atmosphere of purified argon using stan-



SCHEME 3 Plausible deprotonation equilibrium of diethyl phosphite in the presence of $Ln(OAr)_3(THF)_2$.

dard Schlenk techniques. $Ln(OAr)_3(THF)_2$ [87, 88], $Ln[N(SiMe_3)_2]_3$ [89], and $[(Me_3Si)_2N]_3Ln(\mu\text{-Cl})Li(THF)_3$ [61–63] were synthesized according to the literature method. Chalcones were prepared according to published procedures [90]. Diethyl phosphite was purchased from Lianyungang Shengnan Chemical Co., Lianyungang, Jiangsu Province, China. ^{1}H and ^{13}C NMR spectra were obtained on Varian INOVA-400 and System-300 spectrometers using tetramethylsilane (TMS) as an internal reference. Infrared (IR) spectra were obtained on a Nicolet FT-IR 1000 spectrophotometer. High resolution mass spectrometry (HRMS) data were obtained on a Micromass GCT instrument.

Representative Procedure for the Synthesis of γ-Oxophosphonate

A mixture of chalcone (210 mg, 1 mmol), diethyl phosphite (165 mg, 1.2 mmol), and $Yb(OAr^1)_3(THF)_2$ [Ar^1 = 2,6-(^{t}Bu)$_2$–4-MeC_6H_2] (50 mg, 0.05 mmol) in tetrahydrofuran (2.0 mL) was stirred for 5 h at 25°C. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by chromatography on silica gel [eluant: EtOAc/petroleum ether (60–90°C) 1:2] to afford pure product **3a** (318 mg, 92%) as a colorless oil.

Representative Procedure for the Synthesis of 1,2-Oxaphospholane-5-Phosphonate

A mixture of chalcone (210 mg, 1 mmol), diethyl phosphite (415 mg, 3 mmol), and $[(Me_3Si)_2N]_3La(\mu\text{-Cl})Li(THF)_3$ (35 mg, 0.04 mmol) in mixed solvent of toluene/HMPA (5:1, 2.0 mL) was stirred for 5 h at 40°C. Water was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, concentrated

in vacuo, and purified by chromatography on silica gel [eluant: EtOAc/petroleum ether (60–90°C) 1:1] to afford pure product **4a** (350 mg, 80%) as a colorless oil.

*Diethyl 3-oxo-1,3-diphenylpropylphosphonate (**3a**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.46–7.42 (m, 4H), 7.31–7.20 (m, 3 H), 4.17–3.87 (m, 4 H), 3.81–3.63 (m, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.08 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 3-oxo-3-phenyl-1-o-tolylpropylphosphonate (**3b**)*. White solid, melting point (mp) 95–96°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.2 Hz, 1 H), 7.46–7.42 (m, 3 H), 7.17–7.08 (m, 3 H), 4.27–4.18 (m, 1 H), 4.12–4.02 (m, 2 H), 3.88–3.79 (m, 2 H), 3.72–3.58 (m, 2 H), 2.55 (s, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.04 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.3 (d, J = 13.6 Hz), 137.6 (d, J = 7.7 Hz), 136.3, 134.2 (d, J = 6.8 Hz), 133.1, 130.2, 128.4, 127.9, 127.4 (d, J = 4.2 Hz), 126.8 (d, J = 2.7 Hz), 125.9 (d, J = 2.6 Hz), 62.8 (d, J = 6.7 Hz), 61.7 (d, J = 7.2 Hz), 39.5, 33.8 (d, J = 139.6 Hz), 20.0, 16.2 (d, J = 6.0 Hz), 16.0 (d, J = 5.6 Hz) ppm. HRMS (electrospray ionization, ESI): calcd. for $C_{20}H_{25}O_4P$ $[M + H]^+$ 361.1563, found 361.1577. IR: ν = 2982, 2903, 1689, 1596, 1493, 1447, 1392, 1251, 961, 776, 734, and 713 cm^{-1}.

*Diethyl 1-(2-methoxyphenyl)-3-oxo-3-phenylpropylphosphonate (**3c**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.53 (t, J = 7.2 Hz, 1 H), 7.45–7.41 (m, 3 H), 7.19 (t, J = 7.6 Hz, 1 H), 6.90–6.86 (m, 2 H), 4.66–4.57 (m, 1 H), 4.11–4.08 (m, 2 H), 3.95–3.69 (m, 4 H), 3.87 (s, 3 H), 1.27 (t, J = 7.2 Hz, 3 H), 1.09 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 3-oxo-3-phenyl-1-p-tolylpropylphosphonate (**3d**)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.2 Hz, 2 H), 7.54 (t, J = 7.2 Hz, 1 H), 7.43 (t, J = 7.6 Hz, 2 H), 7.32 (dd, J = 8.0, 2.0 Hz, 2 H), 7.09 (d, J = 7.6 Hz, 2 H), 4.12–4.02 (m, 2 H), 3.98–3.87 (m, 2 H), 3.78–3.61 (m, 3 H), 2.28 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.10 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 196.6 (d, J = 15.5 Hz), 137.0 (d, J = 3.5 Hz), 136.7, 133.4, 132.8 (d, J = 7.5 Hz), 129.3, 129.2 (d, J = 7.0 Hz), 128.7, 128.2, 63.1 (d, J = 7.7 Hz), 62.1 (d, J = 7.9 Hz), 39.2, 38.7 (d, J = 140 Hz), 21.2, 16.5 (d, J = 6.4 Hz), 16.4 (d, J = 6.3 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{25}O_4P$ $[M + H]^+$ 361.1563, found 361.1559. IR: ν = 2971, 2931, 1690, 1515, 1466, 1380, 1234, 1025, 953, 817, 757, and 690 cm^{-1}.

*Diethyl 1-(4-methoxyphenyl)-3-oxo-3-phenylpropylphosphonate (**3e**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, J = 7.6 Hz, 2 H), 7.55 (t, J = 7.6 Hz, 1 H), 7.46–7.35 (m, 4 H), 6.83 (d, J = 8.4 Hz, 2 H), 4.11–3.87 (m, 4 H), 3.76 (s, 3 H), 3.74–3.63 (m, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.11 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 1-(4-chlorophenyl)-3-oxo-3-phenylpropylphosphonate (**3f**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.0 Hz, 2 H), 7.56 (t, J = 7.2 Hz, 1 H), 7.47–7.26 (m, 6 H), 4.14–4.05 (m, 2 H), 3.99–3.89 (m, 2 H), 3.83–3.61 (m, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.13 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 1-(4-bromophenyl)-3-oxo-3-phenylpropylphosphonate (**3g**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.47–7.27 (m, 6 H), 4.15–3.87 (m, 4 H), 3.84–3.60 (m, 3 H), 1.29 (t, J = 7.2 Hz, 3 H), 1.13 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 1-(naphthalen-1-yl)-3-oxo-3-phenylpropylphosphonate (**3h**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (d, J = 8.0 Hz, 1 H), 7.95 (d, J = 7.6 Hz, 2 H), 7.83 (d, J = 8.0 Hz, 1 H), 7.75–7.43 (m, 8 H), 4.94 (d, J = 22.4 Hz, 1 H), 4.12–4.06 (m, 2 H), 3.91 (dd, J = 10.4, 6.8 Hz, 2 H), 3.78–3.68 (m, 1 H), 3.42–3.36 (m, 1 H), 1.26 (t, J = 7.2 Hz, 3 H), 0.79 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 3-oxo-1-phenyl-3-p-tolylpropylphosphonate (**3i**)*. White solid, mp 76–77°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, J = 8.1 Hz, 2 H), 7.45–7.42 (m, 2 H), 7.31–7.22 (m, 5 H), 4.10–3.86 (m, 4 H), 3.80–3.63 (m, 3 H), 2.39 (s, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.08 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.1 (d, J = 14.6 Hz), 144.2, 136.2, 136.1, 134.3, 129.4, 128.6, 128.3, 127.3, 63.0 (d, J = 7.1 Hz), 62.1 (d, J = 7.3 Hz), 39.2 (d, J = 139 Hz), 39.1, 21.8, 16.5 (d, J = 4.1 Hz), 16.3 (d, J = 5.0 Hz) ppm. HRMS (ESI): calcd. for $C_{20}H_{25}O_4P$ $[M + H]^+$ 361.1563, found 361.1568. IR: ν = 3061, 2979, 2909, 2889, 1678, 1606, 1501, 1458, 1393, 1237, 1049, 950, 812, 755, and 700 cm^{-1}.

*Diethyl 3-(4-methoxyphenyl)-3-oxo-1-phenylpropylphosphonate (**3j**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (d, J = 8.4 Hz, 2 H), 7.44 (d, J = 7.2 Hz, 2 H), 7.31–7.21 (m, 3 H), 6.90 (d, J = 8.8 Hz, 2 H), 4.10–3.89 (m, 4 H), 3.84 (s, 3 H), 3.76–3.58 (m, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.07 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 3-(4-chlorophenyl)-3-oxo-1-phenylpropylphosphonate (**3k**)* [54]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.88 (d, J = 8.0 Hz, 2 H), 7.42–7.40 (m, 4 H), 7.32–7.21 (m, 3 H), 4.10–3.85 (m, 4 H), 3.76–3.60 (m, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.07 (t, J = 7.2 Hz, 3 H) ppm.

*Diethyl 3-(4-bromophenyl)-3-oxo-1-phenylpropylphosphonate (**3l**)*. White solid, mp 73–74°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.8 Hz, 2 H), 7.58 (d, J = 8.4 Hz, 2 H), 7.43–7.41 (m, 2 H), 7.38–7.27 (m, 3 H), 4.11–4.03 (m, 2 H), 3.98–3.87 (m, 2 H), 3.74–3.59 (m, 3 H), 1.28 (t, J = 7.2 Hz, 3 H), 1.07 (t,

J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 195.6 (d, J = 15.4 Hz), 135.9 (d, J = 7.3 Hz), 135.4, 132.1, 129.7, 129.3 (d, J = 7.2 Hz), 128.7 (d, J = 2.4 Hz), 127.5 (d, J = 3.1 Hz), 63.2 (d, J = 7.7 Hz), 62.2 (d, J = 7.8 Hz), 39.2, 39.1 (d, J = 140 Hz), 16.5 (d, J = 6.5 Hz), 16.3 (d, J = 6.2 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{22}BrO_4P$ $[M + H]^+$ 425.0512, found 425.0501. IR: ν = 3061, 2991, 2929, 1685, 1586, 1500, 1433, 1397, 1251, 1031, 951, 862, 810, 788, 732, and 701 cm^{-1}.

*Diethyl 1,3-bis(4-chlorophenyl)-3-oxopropylphosphonate (***3m***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.77 (d, J = 6.8 Hz, 2 H), 7.33–7.27 (m, 4 H), 7.18–7.17 (m, 2 H), 4.02–3.98 (m, 2 H), 3.88–3.78 (m, 2 H), 3.72–3.54 (m, 3 H), 1.20 (t, J = 7.2 Hz, 3 H), 1.03 (t, J = 7.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.9 (d, J = 15.2 Hz), 139.8, 134.6, 134.4 (d, J = 6.9 Hz), 133.1 (d, J = 3.5 Hz), 130.5 (d, J = 6.5 Hz), 129.4, 128.9, 128.6, 63.0 (d, J = 6.9 Hz), 62.1 (d, J = 7.1 Hz), 38.9, 38.4 (d, J = 140 Hz), 16.3 (d, J = 5.8 Hz), 16.2 (d, J = 5.5 Hz) ppm. HRMS (ESI): calcd. for $C_{19}H_{21}Cl_2O_4P$ $[M + H]^+$ 415.0627, found 415.0618. IR: ν = 2983, 2911, 1690, 1589, 1491, 1385, 1245, 1094, 1050, 829, and 797 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3,5-diphenyl-1,2-oxaphospholan-5-yl)phosphonate (***4a***)*. Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.29 (m, 10 H), 4.35–3.48 (m, 7 H), 3.33–2.74 (m, 2 H), 1.44–1.36 (m, 3 H), 1.32–0.93 (m, 6 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 42.7 (d, J = 30.1 Hz, major diastereomer), 40.7 (d, J = 12.6 Hz, minor diastereomer), 19.5 (d, J = 12.6 Hz, minor diastereomer), 17.6 (d, J = 30.1 Hz, major diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{28}O_6P_2$ $[M + H]^+$ 439.1434, found 439.1436. IR: ν = 3061, 3030, 2983, 2932, 2870, 1602, 1496, 1449, 1392, 1260, 1024, 764, and 699 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-(4-chlorophenyl)-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4b***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–7.29 (m, 9 H), 4.38–3.47 (m, 7 H), 3.31–2.69 (m, 2 H), 1.43–0.98 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 42.1 (d, J = 30.3 Hz, minor diastereomer), 39.8 (d, J = 12.7 Hz, major diastereomer), 19.3 (d, J = 12.7 Hz, major diastereomer), 17.4 (d, J = 30.3 Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{27}ClO_6P_2$ $[M + H]^+$ 473.1044, found 473.1047. IR: ν = 3061, 2983, 2907, 1493, 1447, 1386, 1246, 1095, 1029, 861, 795, 766, and 701 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-(4-bromophenyl)-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4c***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.21 (m, 9 H), 4.33–3.50 (m, 7 H), 3.29–2.71 (m, 2 H), 1.42–0.98 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 40.8 (d, J = 30.3 Hz, minor diastereomer), 38.5 (d, J = 13.3 Hz, major diastereomer), 18.2 (d, J = 13.3 Hz, major diastereomer), 16.2 (d, J = 30.3 Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{27}BrO_6P_2$ $[M + H]^+$ 517.0539, found 517.0530. IR: ν = 3063, 2988, 2908, 2852, 1600, 1492, 1446, 1393, 1283, 1033, 864, 822, 793, 764, and 699 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-p-tolyl-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4d***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–7.03 (m, 9 H), 4.24–3.40 (m, 7 H), 3.24–2.66 (m, 2 H), 2.22 (s, 3 H), 1.33–1.03 (m, 7 H), 0.90–0.87 (m, 2 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 41.8 (d, J = 30.1 Hz, minor diastereomer), 39.8 (d, J = 12.6 Hz, major diastereomer), 18.4 (d, J = 12.6 Hz, major diastereomer), 16.5 (d, J = 30.1 Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{22}H_{30}O_6P_2$ $[M + H]^+$ 453.1590, found 453.1590. IR: ν = 3060, 2978, 2910, 2867, 1602, 1495, 1448, 1397, 1242, 1054, 972, 817, 794, 746, and 702 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-(4-methoxyphenyl)-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4e***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66–6.84 (m, 9 H), 4.34–3.48 (m, 10 H), 3.29–2.70 (m, 2 H), 1.43–1.12 (m, 7 H), 1.01–0.98 (m, 2 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 43.1 (d, J = 29.8 Hz, minor diastereomer), 40.9 (d, J = 12.6 Hz, major diastereomer), 19.6 (d, J = 12.6 Hz, major diastereomer), 17.6 (d, J = 29.8 Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{22}H_{30}O_7P_2$ $[M + H]^+$ 469.1540, found 469.1557. IR: ν = 2990, 1608, 1511, 1460, 1251, 1029, 859, 758, and 698 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-(4-dimethylaminophenyl)-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4f***)*. Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.58–6.59 (m, 9 H), 4.25–3.38 (m, 7 H), 3.21–2.62 (m, 2 H), 2.85 (s, 6 H), 1.35–0.92 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 42.2 (d, J = 29.2 Hz, major diastereomer), 40.3 (d, J = 12.6 Hz, minor diastereomer), 18.6 (d, J = 12.6 Hz, minor diastereomer), 16.6 (d, J = 29.2 Hz, major diastereomer) ppm. HRMS (ESI): calcd. for $C_{23}H_{33}NO_6P_2$ $[M + H]^+$ 482.1856, found 482.1857. IR: ν = 2920, 1608, 1579, 1509, 1448, 1245, 1023, 863, and 701 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-o-tolyl-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (***4g***)*. Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76–7.15 (m, 9 H), 4.39–3.80 (m, 6 H), 3.77–3.30 (m, 2 H), 2.96–2.73 (m, 1 H), 2.43–2.29 (m, 3 H), 1.40–1.02 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): δ = 42.9 (d, J = 30.5 Hz, major diastereomer), 39.9 (d, J = 11.4 Hz, minor diastereomer), 19.7 (d, J = 11.4 Hz, minor

diastereomer), 17.6 (d, $J = 30.5$ Hz, major diastereomer) ppm. HRMS (ESI): calcd. for $C_{22}H_{30}O_6P_2$ [M + H]$^+$ 453.1590, found 453.1598. IR: $\nu = 3061$, 2982, 2930, 2870, 1603, 1493, 1448, 1391, 1262, 1019, 795, 761, and 699 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-(naphthalen-1-yl)-5-phenyl-1,2-oxaphospholan-5-yl)phosphonate (**4h**).* White solid, mp 118–119°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.43$–7.36 (m, 12 H), 5.05–4.94 (m, 1 H), 4.44–4.27 (m, 2 H), 3.99–3.83 (m, 5 H), 3.21–3.07 (m, 1 H), 1.50–0.79 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 39.3$ (d, $J = 27.3$ Hz, minor diastereomer), 38.7 (d, $J = 11.1$ Hz, major diastereomer), 18.6 (d, $J = 11.1$ Hz, major diastereomer), 16.9 (d, $J = 27.3$ Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{25}H_{30}O_6P_2$ [M + H]$^+$ 489.1590, found 489.1591. IR: $\nu = 2981$, 1494, 1446, 1248, 1021, 848, 803, 780, 740, and 700 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-phenyl-5-(4-methoxyphenyl)-1,2-oxaphospholan-5-yl)phosphonate (**4i**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.50$–6.85 (m, 9 H), 4.26–3.37 (m, 10 H), 3.25–2.65 (m, 2 H), 1.36–0.86 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 42.8$ (d, $J = 31.7$ Hz, minor diastereomer), 40.8 (d, $J = 13.2$ Hz, major diastereomer), 19.7 (d, $J = 13.2$ Hz, major diastereomer), 17.8 (d, $J = 31.7$ Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{22}H_{30}O_7P_2$ [M + H]$^+$ 469.1540, found 469.1559. IR: $\nu = 2981$, 2931, 1609, 1499, 1440, 1385, 1251, 1029, 949, 862, 794, and 700 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-phenyl-5-(4-chlorophenyl)-1,2-oxaphospholan-5-yl)phosphonate (**4j**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$–7.27 (m, 9 H), 4.35–2.69 (m, 9 H), 1.43–0.94 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 42.6$ (d, $J = 29.9$ Hz, major diastereomer), 40.6 (d, $J = 12.6$ Hz, minor diastereomer), 19.0 (d, $J = 12.6$ Hz, minor diastereomer), 17.1 (d, $J = 29.9$ Hz, major diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{27}ClO_6P_2$ [M + H]$^+$ 473.1044, found 473.1047. IR: $\nu = 3064$, 2984, 2907, 2868, 1600, 1493, 1448, 1394, 1273, 1095, 1026, 942, 860, 790, 757, and 700 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-phenyl-5-(4-bromophenyl)-1,2-oxaphospholan-5-yl)phosphonate (**4k**).* Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.63$–7.27 (m, 9 H), 4.34–2.71 (m, 9 H), 1.43–0.94 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 41.4$ (d, $J = 29.0$ Hz, minor diastereomer), 39.5 (d, $J = 12.1$ Hz, major diastereomer), 17.7 (d, $J = 12.1$ Hz, major diastereomer), 15.8 (d, $J = 29.0$ Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{27}BrO_6P_2$ [M + H]$^+$ 517.0539, found 517.0537. IR: $\nu = 2980$, 2854, 1602, 1262, 1031, 860, 767, and 698 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3,5-bis(4-chlorophenyl)-1,2-oxaphospholan-5-yl)phosphonate (**4l**).* White solid, mp 153–154°C. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.68$–7.26 (m, 8 H), 4.33–3.46 (m, 7 H), 3.24–2.66 (m, 2 H), 1.42–0.99 (m, 9 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$) $\delta = 40.9$ (d, $J = 29.0$ Hz, minor diastereomer), 38.6 (d, $J = 12.1$ Hz, major diastereomer), 17.7 (d, $J = 12.1$ Hz, major diastereomer), 15.8 (d, $J = 29.0$ Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{21}H_{26}Cl_2O_6P_2$ [M + H]$^+$ 507.0654, found 507.0647. IR: $\nu = 3061$, 2985, 2907, 2868, 1598, 1492, 1443, 1392, 1261, 1032, 948, 821, and 746 cm^{-1}.

*Diethyl (2-ethoxy-2-oxido-3-phenyl-5-methyl-1,2-oxaphospholan-5-yl)phosphonate (**4m**).* Colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.31$–7.20 (m, 5 H), 4.27–3.83 (m, 6 H), 3.73–3.30 (m, 1 H), 3.02–2.79 (m, 1 H), 2.49–2.30 (m, 1 H), 1.66–1.58 (m, 3 H), 1.33–1.18 (m, 7 H), 0.99–0.94 (m, 2 H) ppm. ^{31}P NMR (121 MHz, $CDCl_3$): $\delta = 43.4$ (d, $J = 33.3$ Hz, minor diastereomer), 40.9 (d, $J = 13.8$ Hz, major diastereomer), 22.3 (d, $J = 13.8$ Hz, major diastereomer), 21.4 (d, $J = 33.3$ Hz, minor diastereomer) ppm. HRMS (ESI): calcd. for $C_{16}H_{26}O_6P_2$ [M + H]$^+$ 377.1277, found 377.1280. IR: $\nu = 3030$, 2983, 2934, 2871, 1602, 1497, 1450, 1391, 1245, 970, 813, 761, and 700 cm^{-1}.

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