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# Catalytic Lewis acid phosphorylation with pyrophosphates

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ABSTRACT

We report a method for the Lewis acid catalyzed phosphorylation of alcohols with pyrophosphates. $Ti(O^tBu)_4$ was found to be the most effective catalyst in the phosphorylation of both primary and secondary alcohols with tetrabenzylpyrophosphate, providing conversions between 54% and >98% and isolated yields between 50% and 97%. Other pyrophosphates with orthogonal protecting groups were synthesized and screened to validate the generality of the approach. This study will describe how benzyl, methyl, ethyl, allyl, and *o*-nitrobenzyl pyrophosphates are all effective phosphorylating agents under Lewis acid catalysis.



## 1. Introduction

Phosphate is a ubiquitous functional group found in natural products,[1] drug candidates,[2] and biological messengers.[3] The derivatization of alcohols is the primary method for the synthesis of phosphates. Due to the unique oxidation states of phosphorus (P), this can be accomplished with either P(III) reagents (such as phosphoramidites,[4] phosphites[5] or phosphorochloridites[6]) followed by oxidation[7] or P(V) reagents (such as chlorophosphates[8]). In recent years, most of the attention in phosphorylation has focused on P(III) reagents, particularly the use of phosphoramidites in the synthesis of oligonucleotides.[9]

Catalytic methods for the synthesis of any functional group are beneficial because they can increase reaction rates, reduce the quantity of waste products, and alter the distribution of reaction products. Catalytic reactions for the phosphorylation of alcohols are favorable because they do not require the activation of the alcohol (i.e., formation of an alkoxide) and/or the use of highly reactive phosphorylating reagents that can be difficult to synthesize or handle. Chiral variants of the catalyst can also be developed to desymmetrize or resolve meso or racemic alcohols, respectively, providing enantioselective syntheses of phosphorylated molecules.[10] Our previous work in this area focused on phosphitylation with phosphoramidites utilizing catalytic tetrazole and an isocyanate additive to facilitate catalyst turnover.[11] Recently, our efforts have focused on developing a catalytic P(V) phosphorylation reaction, which removes the need for a subsequent oxidation step. Diphenylchlorophosphate, a common, commercially-available phosphorylating agent, has been used with great success in the phosphorylation of alcohols with catalytic Lewis acids[12] and nucleophiles.[8b] Other commercially available chlorophosphates (i.e., dimethyl and diethyl) have only been demonstrated to work with Lewis acids.[12] Benzyl protecting groups are widely used in phosphate chemistry, however dibenzylchlorophosphate (DBCP) must be synthesized from dibenzylphosphite.[13] In our hands, DBCP was not a competent phosphorylating agent with nucleophilic catalysts[14] and provided inconsistent results under Lewis acid catalysis, most likely due to reagent purity.

In searching for a phosphorylating agent that would be easy to synthesize and purify and available with a diverse range of orthogonal protecting groups, we turned our attention to pyrophosphates. The early literature on pyrophosphates explored the synthesis of nucleotide diphosphates and their use as phosphorylating agents.[15] Perhaps due to their lower reactivity, pyrophosphates have not been used as extensively as their chlorophosphate analogs. We hypothesized that a catalyst could overcome the lower reactivity of pyrophosphates, and that this increased stability would be beneficial in their synthesis and purification. Two general methods exist for the synthesis of pyrophosphates (Scheme 1). The first approach relies on dehydrating a phosphate diester with reagents, such as DCC.[16] Many phosphate diesters are commercially available or can be synthesized in one-step from methyldichlorophosphate.[17] The second method couples a phosphate with a chlorophosphate liberating HCl. This reaction can be accomplished in one pot from the corresponding phosphite with $CCl_4$ as the chlorinating agent in the presence of $K_2CO_3$ and a phase

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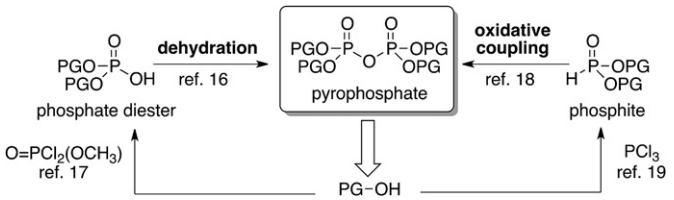
transfer catalyst.[18] As is true in the first method, many phosphites are commercially available or can otherwise be synthesized from phosphorus trichloride.[19] Recently, Han and co-workers published an alternative method for the synthesis of pyrophosphates via a copper catalyzed coupling of phosphites.[20] The multitude of synthetic methods to synthesize pyrophosphates made them an attractive target for developing a phosphorylation reaction with orthogonal protecting groups on the phosphorylating agent.




**Scheme 1.** Synthesis of pyrophosphates.

## 2. Results and discussion

Our pyrophosphate study began with tetrabenzylpyrophosphate (TBPP, Fig. 1), a well-known compound first reported in the 1940s.[8c,21a] Most examples of TBPP as a phosphorylating agent rely on conversion of the alcohol substrate to an alkoxide.[22] One encouraging report used the chelation of a full equivalent of silver oxide and a diol for the monophosphorylation of this diol with TBPP.[23] This stoichiometric reaction suggested to us the possibility of utilizing catalytic Lewis acids with appropriate catalyst turnover. We began our study by screening the phosphorylation of 2-dodecanol under a variety of catalytic conditions with TBPP (Table 1). When no catalyst is added the reaction yields no product as detected by $^{1}$H and $^{31}$P NMR (Table 1, entry 1). When 10 mol % DMAP was used there was also no conversion to product; only recovered starting material was isolated (Table 1, entry 2). Titanium Lewis acids, which have previously been reported with chlorophosphates,[12] yielded 67% and 94% conversion to **1** with Ti(O$^{i}$Pr)$_4$ and Ti(O$^{t}$Bu)$_4$, respectively (Table 1, entry 3–4). The use of the more common Ti(O$^{i}$Pr)$_4$ resulted in lower yields due to competitive phosphorylation of isopropanol formed during ligand exchange. When other Lewis acids were examined, only trace amounts of product or no product was observed (Table 1, entries 5–6).

Upon identifying a competent catalyst for phosphorylation with TBPP, our attention then turned to screening other alcohols to determine the generality of the phosphorylation method. When different secondary alcohols were treated with 10 mol % of Ti(O$^{t}$Bu)$_4$, TBPP and Hünig's Base (as an acid scavenger), phosphorylated products (**1**–**4**) were observed in 86–95% conversion and isolated

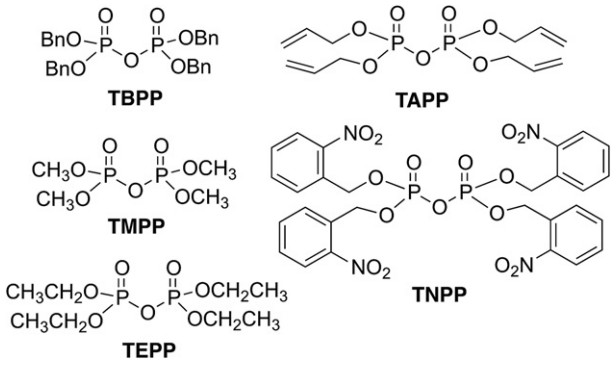
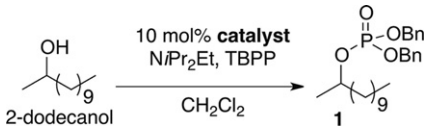



**Fig. 1.** Structure of pyrophosphates explored in this study.

**Table 1**
Catalyst screen for phosphorylation with TBPP[a]




| Entry | Catalyst | Conversion[b] |
|---|---|---|
| 1 | None | 0% |
| 2 | DMAP | 0% |
| 3 | Ti(O$^{i}$Pr)$_4$ | 67% |
| 4 | Ti(O$^{t}$Bu)$_4$ | 94% |
| 5 | Sc(OTf)$_3$ | 9% |
| 6 | Bi(OTf)$_3$ | 0% |

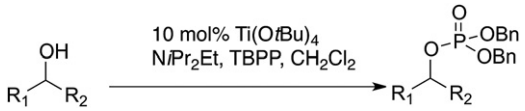
[a] Reactions performed with 1.2 equiv of TBPP and 1.5 equiv of Hünig's base at room termperature for 16 h.
[b] Conversions obtained from integrations of $^{1}$H NMR of crude rxns.

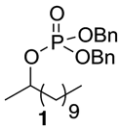
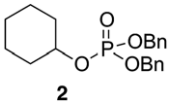
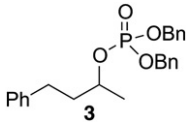
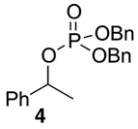
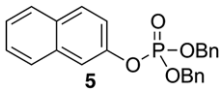
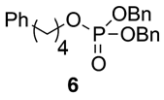
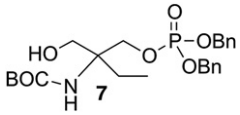
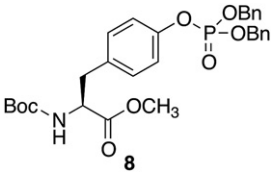
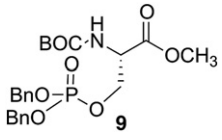
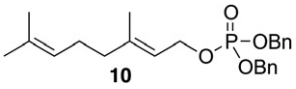
in 80–88% yield (Table 2). In the absence of catalyst, all of the secondary alcohols tested provided exclusively recovered starting material by $^{1}$H and $^{31}$P NMR. Phenolic alcohols were also phosphorylated under these conditions though in lower yield (Table 2, entry 5). Phosphorylation of primary alcohols with TBPP resulted in 26% conversion without catalyst and 98% conversion with 10 mol % Ti(O$^{t}$Bu)$_4$ (Table 2, entry 6). We attribute this to the higher innate reactivity of primary alcohols in phosphorylation reactions.[24] Unfortunately, we found tertiary alcohols did not perform well under our reaction conditions. Butylcyclohexanol and 2-methyl-3-butyn-2-ol did not generate high yields of phosphorylated product at room temperature (negligible product detected by NMR and 26% isolated yield, respectively). When these reactions were heated to reflux in $CH_2Cl_2$, the reaction was accompanied by contaminant phosphorylation of *tert*-butanol derived from ligand exchange with the catalyst.

We were also interested to see if more functionalized alcohols would be amendable to phosphorylation with Ti(O$^{t}$Bu)$_4$. Boc-protected amines, methyl esters and alkenes were all compatible with the reactions conditions (Table 2, entries 7–10). The monophosphorylation of a diol was readily achieved resulting in phosphate **7** in >98% conversion and 93% isolated yield. It should be noted that no diphosphorylated product was isolated even when 2 equiv of pyrophosphate was used.[25] The side chain hydroxyl of the protected amino acids Serine and Tyrosine was phosphorylated to generate **8** and **9** in 71% and 50% yield, respectively. Allylic alcohols were also suitable substrates, as was demonstrated by the phosphorylation of geraniol in 86% yield (Table 2, entry 10).

We recognized an important aspect of this method was its use in the synthesis of phosphorylated alcohols with diverse protecting groups on the phosphate. Methyl phosphates have been selectively deprotected in the presence of other alkyl and aryl groups on phosphate with 1 M TMSOTf–thioanisole in TFA.[26] Under carefully monitored conditions, ethyl phosphonates have been selectively mono-deprotected under acidic and basic conditions.[27] To study these alkyl protecting groups, tetramethylpyrophosphate (TMPP) and tetraethylpyrophosphate (TEPP) were synthesized from the corresponding phosphite (Fig. 1).[18] Phosphorylation of 2-dodecanol with TMPP and 10 mol % Ti(O$^{t}$Bu)$_4$ resulted in 91% isolated yield, however conversion could not be obtained due to overlap in the $^{1}$H NMR of 2-dodecanol and the product (Table 3, entry 1). Phosphorylation with TEPP resulted in lower conversions and yields (Table 3, entry 2), presumably due to the increased steric-bulk around the electrophilic center. The allyl group has been used extensively as an orthogonal protecting group for phosphate in nucleic acid and peptide synthesis.[28] To our knowledge, tetraallylpyrophosphate (TAPP) was a new compound that had not been previously used as a phosphorylating agent (Fig. 1). TAPP was synthesized via both

**Table 2**
Phosphorylation of primary and secondary alcohols with TBPP[a]

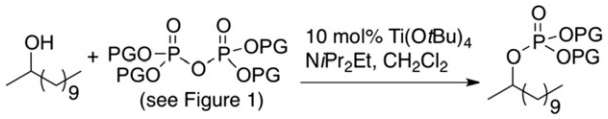


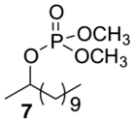
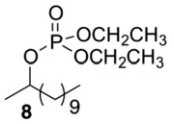
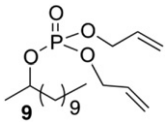
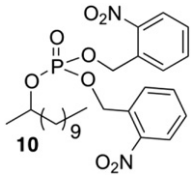

| Entry | Product | Conversion[b] | Isolated yield |
|---|---|---|---|
| 1 |  | 94% | 88% |
| 2 |  | 90% | 86% |
| 3 |  | 86% | 80% |
| 4 |  | 95% | NA[c] |
| 5 |  | NA[d] | 54% |
| 6 |  | 98% | 97% |
| 7 |  | >98% | 93% |
| 8 |  | 54% | 50% |
| 9 |  | 77% | 71% |
| 10 |  | 94% | 86% |

[a] Reactions performed with 1.2 equiv of TBPP and 1.5 equiv of Hünig's base at room temperature for 16 h.
[b] Obtained from $^1$H NMR of crude rxns.
[c] From NMR analysis, product slowly decomposes during column chromatography to styrene and dibenzyl phosphate.
[d] Conversion could not be obtained due to overlap in $^1$H NMR resonance.

methods discussed in Scheme 1 and was used in the phosphorylation of 2-dodecanol with 10 mol % Ti($O^tBu$)$_4$. This resulted in 86% conversion and 84% yield to the desired diallyl protected phosphate (Table 3, entry 3). *o*-Nitrobenzyl esters have been successfully used

**Table 3**
Phosphorylation with orthogonally protected pyrophosphates




| Entry | Product | Conversion[c] | Isolated yield |
|---|---|---|---|
| 1 |  | NA[d] | 91%[a] |
| 2 |  | 54% | 49%[a] |
| 3 |  | 86% | 84%[a] |
| 4 |  | 95% | 92%[b] |

[a] Reactions performed with 1.5 equiv of pyrophosphate and 1.8 equiv of Hünig's base at room temperature for 16 h.
[b] Reactions performed with 1.2 equiv of pyrophosphate and 1.5 equiv of Hünig's base at room temperature for 16 h.
[c] Conversions obtained from integrations of $^1$H NMR of crude rxns.
[d] Conversion could not be obtained due to overlap in $^1$H NMR resonance.

as phosphate protecting groups that are removed under photolysis.[29] Since light is the only reagent necessary for the deprotection, this type of 'caging group' has witnessed great success in blocking biologically active molecules, such as phosphopeptides, and proteins, nucleic acids, and small molecule messengers.[30] In these studies, the caged phosphate is released at specific times in cellular or biochemical experiments. To our knowledge, tetra-*o*-nitrobenzylpyrophosphate (TNPP) was also a new compound that we attempted to synthesize via both pyrophosphate methods (Fig. 1). In our hands, only the dehydration of di-*o*-nitrobenzylphosphate resulted in good yields of TNPP. Once again, this new pyrophosphate was successful in the phosphorylation of 2-dodecanol in the presence of 10 mol % catalyst yielding 95% conversion and 92% isolated yield of the caged phosphorylated alcohol.

## 3. Conclusions

This study has demonstrated that pyrophosphates are versatile phosphorylating agents when combined with titanium Lewis acids. Both primary and secondary alcohols were phosphorylated in good conversions and yields using pyrophosphates protected with benzyl, methyl, ethyl, allyl, and *o*-nitrobenzyl groups. Catalytic Lewis acids facilitated the use of the less reactive but more robust pyrophosphates to serve as competent phosphorylating agents. All pyrophosphates screened to date have been successful phosphorylating agents under the conditions described. We will continue to develop other pyrophosphates and screen catalysts capable of performing this important transformation.

## 4. Experimental

### 4.1. General procedures

Proton NMR spectra were recoded on Varian 400 spectrometer. Proton chemical shifts are reported in parts per million ($\delta$) relative to internal tetramethylsilane (TMS, $\delta$ 0.0) or with the solvent reference relative to TMS employed as the internal standard ($CDCl_3$, $\delta$ 7.26 ppm; DMSO-$d_6$, $\delta$ 2.50; $C_6D_6$ $\delta$ 7.16 ppm; $D_2O$, $\delta$ 4.79). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m)], coupling constants [Hz], integration). Carbon NMR spectra were recorded on Varian 400 (100 MHz) with complete proton decoupling. Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ 77.0). Phosphorus NMR spectra were recorded on a Varian 400 (162 MHz) spectrometer with complete proton decoupling. Phosphorus chemical shifts are reported in ppm ($\delta$) relative to an 85% $H_3PO_4$ external standard. NMR data were collected at 25 °C, unless otherwise indicated. Infrared spectra were obtained on a Perkin Elmer SpectrumOne FTIR spectrometer with a universal ATR sampling accessory. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F254 precoated plates (0.25 mm thickness). TLC $R_f$ values are reported. Visualization was accomplished by irradiation with a UV lamp and/or staining with cerium ammonium molybdenate (CAM) solution. Flash column chromatography was performed using Silica Gel 60 Å (40 μm).[31] High-resolution mass spectra were obtained at the Mass Spectrometry Facility at the University of Massachusetts at Amherst (Amherst, MA) or University of Illinois at Urbana Champaign (Urbana, IL). The method of ionization is given in parentheses. All reactions were carried out under a nitrogen atmosphere employing oven- and/or flame-dried glassware at room temperature unless otherwise stated. All solvents were obtained from a MBraun solvent purification system (MB-SPS). 2-((*tert*-Butoxycarbonyl)amino)-2-ethyl-1,3-propanediol was synthesized following a literature procedure.[32] Tetrabenzylpyrophosphate (TBPP) was synthesized following a modified literature procedure from dibenzyl phosphate[16] or dibenzylphosphite.[18] Tetraethylpyrophosphate (TEPP) and Tetramethylpyrophosphate (TMPP) were synthesized from the corresponding phosphite.[18] All other chemicals were obtained from Aldrich and used without further purification.

### 4.2. General procedure for the phosphorylation of alcohols with TBPP

The alcohol (0.49 mmol) was dissolved in 1.0 mL of $CH_2Cl_2$. *N*,*N*-Diisopropylethylamine (0.130 mL, 0.746 mmol) was added to the solution, followed by tetrabenzylpyrophosphate (0.320 g, 0.594 mmol). $Ti(O^tBu)_4$ (19 μL, 0.049 mmol, 10 mol %) was added and the reaction was stirred for 16 h at room temperature. The solution was then vacuum filtered through a 20:1 Silica/$MgSO_4$ plug and washed with 50 mL of 1:1 EtOAc/petroleum ether. The filtrate was concentrated under reduced pressure and a crude NMR was obtained for conversion. The crude product was purified using silica gel chromatography. See Table 2 for conversion and yield data.

*4.2.1. 2-Dodecyl dibenzyl phosphate* ***1***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.35–7.33 (m, 10H), 5.03 (m, 4H), 4.50 (m, 1H), 1.61 (m, 1H), 1.48 (m, 1H), 1.37–1.23 (m, 19H), 0.88 (t, $J$=6.88 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 139.5, 136.0, 136.0, 135.9, 128.7, 128.5, 128.3, 127.7, 127.7, 122.2, 118.9, 76.7 (d, $J$=6.1 Hz), 68.9 (d, $J$=6.1 Hz), 37.4 (d, $J$=3.1 Hz), 31.9, 29.6, 29.5, 29.5, 29.3, 29.3, 25.1, 22.6, 21.5 (d, $J$=3.1 Hz) 14.1; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −0.5; IR (film, cm$^{-1}$) 2924, 2854, 1597, 1498, 1455, 1380, 1264, 1214; TLC $R_f$ 0.45 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{26}H_{39}O_4P+H]^+$ requires $m/z$ 447.2664. Found 447.2676 (FAB).

*4.2.2. Cyclohexyl dibenzyl phosphate* ***2***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.36–7.31 (m, 10H), 5.03 (m, 4H), 4.36 (m, 1H), 1.88 (m, 2H), 1.71 (m, 2H), 1.54–1.43 (m, 3H), 1.33–1.20 (m, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 136.3 (d, $J$=6.8 Hz), 128.8, 128.6, 128.1, 77.9 (d, $J$=6.0 Hz), 69.2 (d, $J$=6.1 Hz), 33.5 (d, $J$=4.6 Hz), 25.3, 23.7; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −0.6; IR (film, cm$^{-1}$) 2937, 2859, 1497, 1455, 1259, 1214; TLC $R_f$ 0.31 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{20}H_{25}O_4P+H]^+$ requires $m/z$ 361.1569. Found 361.1536 (FAB).

*4.2.3. 2-(4-Phenylbutyl) dibenzyl phosphate* ***3***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.37–7.31 (m, 10H), 7.28–7.13 (m, 5H), 5.05 (m, 4H), 4.55 (m, 1H), 2.66 (m, 2H), 1.96 (m, 1H), 1.81 (m, 1H), 1.35 (d, $J$=6.0 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 141.2, 135.9 (d, $J$=8.4 Hz), 128.4, 128.3 (d, $J$=3.1 Hz), 128.2, 127.7, 125.8, 75.8 (d, $J$=6.1 Hz), 69.0 (d, $J$=2.3 Hz), 68.9 (d, $J$=3.1 Hz), 39.0 (d, $J$=6.8 Hz), 31.3, 21.4 (d, $J$=2.3 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −0.4; IR (film, cm$^{-1}$) 3030, 2931, 1497, 1455, 1381, 1263; TLC $R_f$ 0.33 (50% ether/petroleum ether); Exact mass calcd for $[C_{24}H_{27}O_4P+H]^+$ requires $m/z$ 411.1725. Found 411.1757 (FAB).

*4.2.4. sec-Phenethyl dibenzyl phosphate* ***4***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.35–7.27 (m, 13H), 7.19 (m, 2H), 5.49 (m, 1H), 4.98 (m, 2H), 4.86 (d, $J$=7.6 Hz, 2H), 1.59 (d, $J$=6.6 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 141.2 (d, $J$=2.3 Hz), 135.6 (d, $J$=3.0 Hz), 135.5 (d, $J$=3.0 Hz), 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.6, 127.5, 125.7, 76.9, 76.5, 68.8, 68.8, 68.7, 23.9 (d, $J$=5.3 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −0.6; IR (film, cm$^{-1}$) 3033, 1497, 1455, 1378, 1265, 1212; TLC $R_f$ 0.32 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{22}H_{23}O_4P+H]^+$ requires $m/z$ 383.1412. Found 383.1441 (FAB).

*4.2.5. 2-Naphthyl dibenzyl phosphate* ***5***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.81 (dd, $J$=7.8 Hz, $J$=1.2 Hz, 1H), 7.78 (d, $J$=9.0 Hz, 1H), 7.71 (dd, $J$=7.8 Hz, $J$=1.3 Hz, 1H), 7.57 (observed s, 1H), 7.46 (dquintets, $J$=7.6 Hz, $J$=1.9 Hz, 2H), 7.33 (m, 10H), 7.28 (ddd, $J$=8.9 Hz, $J$=2.5 Hz, $J$=0.7 Hz, 1H) 5.16 (d, $J$=8.3 Hz, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 148.1 (d, $J$=7.2 Hz), 135.5, 135.4, 138.8 (d, $J$=0.8 Hz), 130.9 (d, $J$=0.8 Hz), 129.8, 128.7, 128.6, 128.1 (2C), 127.7, 127.6, 126.7, 125.5, 70.1 (d, $J$=5.5 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −6.1; IR (film, cm$^{-1}$) 3034, 1632, 1599, 1510, 1497, 1464, 1456, 1381, 1279, 1244; TLC $R_f$ 0.36 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{24}H_{21}O_4P+H]^+$ requires $m/z$ 405.1256. Found 405.1210 (FAB).

*4.2.6. 4-Phenylbutyl dibenzyl phosphate* ***6***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.33 (m, 10H), 7.29–7.12 (m, 5H), 5.03 (m, 4H), 4.00 (m, 2H), 2.59 (m, 2H), 1.64 (m, 4H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 141.7, 135.7 (d, $J$=6.9 Hz), 128.4, 128.3, 128.2 (d, $J$=5.3 Hz), 127.8, 125.7, 69.0 (d, $J$=5.4 Hz), 67.5 (d, $J$=6.1 Hz), 35.1, 29.5, 29.4, 27.0; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 0.3; IR (film, cm$^{-1}$) 3029, 2942, 1496, 1454, 1380, 1275; TLC $R_f$ 0.27 (50% ether/petroleum ether); Exact mass calcd for $[C_{24}H_{27}O_4P+H]^+$ requires $m/z$ 411.1725. Found 411.1686 (FAB).

*4.2.7. 2-(tert-Butoxycarbonyl)amino-2-ethyl-3-hydroxylpropyl dibenzyl phosphate* ***7***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.41–7.31 (m, 10H), 5.05 (dd, $J$=8.6 Hz, $J$=2.4 Hz, 4H), 4.73 (s, NH), 4.10 (m, 2H), 3.54 (s, 2H), 1.75 (m, 1H), 1.47 (m, 1H), 1.42 (s, 9H), 0.81 (t, $J$=7.4, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 155.6, 135.5 (d, $J$=3.9 Hz), 128.7, 128.6, 128.0, 79.8, 69.6 (d, $J$=6.0 Hz), 67.9 (d, $J$=6.0 Hz), 64.1, 58.9 (d, $J$=6.4 Hz), 28.3, 24.4, 7.3; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 0.2; IR (film, cm$^{-1}$) 3417, 3314, 2971, 1712, 1497, 1456, 1391, 1366, 1247; TLC $R_f$ 0.29 (30% ethyl acetate/30% methylene chloride/40% toluene);

Exact mass calcd for $[C_{24}H_{34}NO_7P+H]^+$ requires *m*/*z* 480.2151. Found 480.2145 (ESI).

*4.2.8. (s)-Boc-Tyr(dibenzylphosphate)-methyl ester* ***8***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.36–7.31 (m, 10H), 7.06 (m, 4H), 5.12 (dd, *J*=2.1 Hz, *J*,=6.3 Hz, 4H), 4.97 (d, *J*=8.2 Hz, 1H), 4.56 (m, 1H), 3.70 (s, 3H), 3.08 (dd, *J*=12.5 Hz, *J*=4.7 Hz, 1H), 3.01 (dd, *J*=14 Hz, *J*=6 Hz, 1H), 1.43 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 172.1, 155.0, 149.6 (d, *J*=7.5 Hz), 135.4 (d, *J*=5.2 Hz), 132.9, 130.5 (d, *J*=24.3 Hz), 128.8 (d, *J*=3.2 Hz), 128.4 (d, *J*=6.8 Hz), 128.1 (d, *J*=29.6 Hz), 120.1 (d, *J*=29.1 Hz), 80.0, 69.9 (d, *J*=5.6 Hz), 54.3, 52.3 (d, *J*=19.5 Hz), 37.5, 28.3 (d, *J*=17.6 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −6.3; IR (film, $cm^{-1}$) 2976, 1747, 1712, 1507, 1456, 1366, 1250; TLC $R_f$ 0.24 (65% ether/hexanes); Exact mass calcd for $[C_{29}H_{34}NO_8P+H]^+$ requires *m*/*z* 556.2100. Found 556.2106 (ESI).

*4.2.9. (s)-Boc-Ser(dibenzylphosphate)-methyl ester* ***9***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.37–7.32 (m, 10H), 5.42 (d, *J*=8.2 Hz, 1H), 5.03 (d, *J*=8.2 Hz, 2H), 5.01 (dd, *J*=2.3 Hz, *J*=8.2 Hz, 2H), 4.48 (m, 1H), 4.40 (m, 1H), 4.21 (m, 1H), 3.71 (s, 3H), 1.44 (s, 9H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 169.7, 155.2, 135.5, 128.8 (d, *J*=2.5 Hz), 128.5 (d, *J*=5.2 Hz), 128.2, 127.8, 80.3, 69.6, 67.5 53.9, 52.7 (d, *J*=21.9 Hz), 28.3 (d, *J*=20.0 Hz); $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −1.1; IR (film, $cm^{-1}$) 3275, 3035, 2982, 2930, 2850, 1732, 1700, 1531, 1456, 1366; TLC $R_f$ 0.32 (20% ethyl acetate/30% methylene chloride/50% toluene); Exact mass calcd for $[C_{23}H_{30}NO_8P+H]^+$ requires *m*/*z* 480.1787. Found 480.1787 (ESI).

*4.2.10. Geranyl dibenzylphosphate* ***10***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 7.35 (m, 10H), 5.34 (m, 1H), 5.04 (m, 1H), 5.03 (d, *J*=7.9 Hz, 4H), 4.54 (t, *J*=7.4 Hz, 2H), 2.04 (m, 4H), 1.67 (s, 3H), 1.64 (s, 3H), 1.59 (s, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 142.9, 135.9 (d, *J*=5.0 Hz), 131.9, 128.7 (d, *J*=9.6 Hz), 128.3 (d, *J*=10.3 Hz), 128.0, 127.7, 123.8, 123.4, 118.7 (d, *J*=6.3 Hz), 118.5 (d, *J*=6.8 Hz), 69.1 (d, *J*=5.6 Hz), 64.4 (d, *J*=5.6 Hz), 39.4, 26.2; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −0.6; IR (film, $cm^{-1}$) 3034, 2920, 1669, 1498, 1455; TLC $R_f$ 0.23 (40% ethyl ether/pentane); Exact mass calcd for $[C_{24}H_{31}O_4P+H]^+$ requires *m*/*z* 415.2038. Found 415.2050 (ESI).

### 4.3. Procedure for the phosphorylation of 2-dodecanol with TMPP and TEPP

The pyrophosphate (0.734 mmol, 1.5 equiv) was dissolved in 1 mL $CH_2Cl_2$. To this flask was added 2-dodecanol (110 μL, 0.489 mmol), *N*,*N*-diisopropylethylamine (157 μL, 0.901 mmol, 1.8 equiv) and lastly Ti(O$^t$Bu)$_4$ (19 μL, 0.05 mmol, 10 mol %). After 18 h, the reaction was vacuum filtered through a 20:1 Silica/$MgSO_4$ plug and washed with 50 mL of 1:1 EtOAc/petroleum ether. The filtrate was concentrated under reduced pressure and a crude NMR was obtained for conversion. The crude product was purified using silica gel chromatography to yield 0.131 g (91% yield) of 2-dodecyl dimethyl phosphate and 0.077 g (49% yield) of 2-dodecyl diethyl phosphate.

*4.3.1. 2-Dodecyl dimethyl phosphate* ***11***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.49 (m, 1H), 3.77 (d, *J*=2.8 Hz, 3H), 3.74 (d, *J*=2.9 Hz, 3H), 1.65 (m, 1H), 1.53 (m, 1H), 1.40–1.26 (m, 19H), 0.88 (t, *J*=6.85 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 76.4 (d, *J*=6.6 Hz), 54.0 (d, *J*=3.6 Hz), 53.9 (d, *J*=3.7 Hz), 37.4 (d, *J*=5.9 Hz), 31.9, 29.6, 29.5, 29.4, 29.3, 29.3, 25.1, 22.6, 21.5 (d, *J*=3.0 Hz), 14.1; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ 0.5; IR (film, $cm^{-1}$) 2924, 2854, 1466, 1381, 1267; TLC $R_f$ 0.26 (35% ethyl acetate/hexanes); Exact mass calcd for $[C_{14}H_{31}O_4P+H]^+$ requires *m*/*z* 295.2038. Found 295.2034 (FAB).

*4.3.2. 2-Dodecyl diethyl phosphate* ***12***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 4.48 (m, 1H), 4.10 (m, 4H), 1.64 (m, 1H), 1.51 (m, 1H), 1.40–1.26 (m, 25H), 0.88 (t, *J*=6.55 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 76.0 (d, *J*=6.0 Hz), 63.4 (d, *J*=2.8 Hz), 63.3 (d, *J*=2.8 Hz), 37.4 (d, *J*=6.4 Hz), 31.8, 29.6, 29.5, 29.4, 29.3, 29.2, 25.1, 22.6, 21.5 (d, *J*=3.2 Hz), 16.1 (d, *J*=2.4 Hz), 16.0 (d, *J*=2.4 Hz), 14.1; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −1.6; IR (film, $cm^{-1}$) 2924, 2854, 1466, 1380, 1262; TLC $R_f$ 0.26 (30% ethyl acetate/hexanes); Exact mass calcd for $[C_{16}H_{35}O_4P+H]^+$ requires *m*/*z* 323.2351. Found 323.2366 (FAB).

### 4.4. Procedure for the phosphorylation of 2-dodecanol with TAPP

Tetraallylpyrophosphate (TAPP) was synthesized according to the following modified literature procedure and used directly in phosphorylation reactions: Diallyl phosphate (3.56 g, 19.97 mmol, 1 equiv) was dissolved in 70 mL of $CH_2Cl_2$. *N*,*N*-Dicyclohexylcarbodiimide (2.268 g, 10.99 mmol, 0.55 equiv) was then added and the reaction stirred for 4 h (dicyclohexylurea immediately begins to precipitate). The reaction mixture was then vacuum filtered to remove the dicyclohexylurea and the filtrate concentrated under reduced pressure. The crude product was resuspended in 40 mL ether, and submitted to a second vacuum filtration to remove any residual DCC and Urea. The filtrate was concentrated under reduced pressure to yield 3.362 g (99.5% yield) of tetraallylpyrophosphate.

Tetraallylpyrophosphate (0.254 g, 0.751 mmol, 1.5 equiv) was then dissolved in 1 mL $CH_2Cl_2$. To this flask was added 2-dodecanol (110 μL, 0.489 mmol), *N*,*N*-diisopropylethylamine (160 μL, 0.919 mmol, 1.9 equiv) and lastly Ti(O$^t$Bu)$_4$ (19 μL, 0.05 mmol, 10 mol %). After 18 h, the reaction was vacuum filtered through a 20:1 Silica/$MgSO_4$ plug and washed with 50 mL of 1:1 EtOAc/petroleum ether. The filtrate was concentrated under reduced pressure and a crude NMR was obtained for conversion. The crude product was purified using silica gel chromatography to yield 142 mg (84% yield) of 2-dodecanol diallyl phosphate as a viscous oil.

*4.4.1. 2-Dodecyl diallyl phosphate* ***13***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 5.94 (m, 2H), 5.37 (dq, *J*=1.5 Hz, *J*=17.2 Hz, 2H), 5.24 (dq, *J*=1.4 Hz, *J*=10.4 Hz, 2H), 4.51 (m, 5H), 1.65 (m, 1H), 1.52 (m, 1H), 1.41–1.26 (m, 19H), 0.88 (t, *J*=6.85 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 132.6 (d, *J*=7.6 Hz), 117.9 (d, *J*=2.0 Hz), 76.5 (d, *J*=6.4 Hz), 67.8 (d, *J*=4.4 Hz), 37.4 (d, *J*=6.0 Hz), 31.9, 29.7, 29.6, 29.5, 29.4, 29.3, 25.1, 22.7, 21.5 (d, *J*=3.2 Hz), 14.1; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −1.5; IR (film, $cm^{-1}$) 2926, 2854, 1461, 1425, 1381, 1266; TLC $R_f$ 0.28 (20% ethyl acetate/hexanes); Exact mass calcd for $[C_{18}H_{35}O_4P+H]^+$ requires *m*/*z* 347.2351. Found 347.2358 (FAB).

### 4.5. Procedure for the phosphorylation of 2-dodecanol with TNPP

Tetra-*o*-nitrobenzylpyrophosphate (TNPP) was synthesized according to the following modified literature procedure and used directly in phosphorylation reactions: di-*o*-nitrobenzylphosphate[17] (1.00 g, 2.72 mmol) was dissolved in 20 ml of $CH_2Cl_2$. *N*,*N*′-Dicyclohexylcarbodiimide (0.340 mg, 1.65 mmol, 0.6 equiv) was added to the solution and the reaction was heated to reflux. After 4 h the reaction was cooled to room temperature and then cooled to −20 °C to ensure complete precipitation of the *N*,*N*-dicyclohexylurea by-product. The precipitate was removed by vacuum filtration and the filtrate was concentrated under reduced pressure to yield 0.860 g (88% yield) of tetra-*o*-nitrobenzylpyrophosphate.

2-dodecanol (110 μL, 0.489 mmol) was dissolved in 1 ml of $CH_2Cl_2$. *N*,*N*-Diisopropylethylamine (130 μL, 0.797 mmol, 1.5 equiv), di-*o*-nitrobenzyl pyrophosphate (427 mg, 0.594 mmol, 1.2 equiv) and lastly Ti(O$^t$Bu)$_4$ (19 μL, 0.05 mmol, 10 mol %) was added to the reaction flask. After 18 h, the reaction was concentrated under reduced pressure and a crude NMR was obtained for conversion. The crude product was purified with silica gel chromatography eluting

with 30% ethyl acetate/hexane to yield 240 mg (92% yield) of 2-dodecyl di-*o*-nitrobenzylphosphate as a viscous oil.

*4.5.1. 2-Dodecyl di-o-nitrobenzylphosphate* ***14***. $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.15 (d, $J$=7.99 Hz, 2H), 7.81 (d, $J$=7.99 Hz, 2H), 7.70 (dt, $J$=7.56 Hz, $J$=1.60 Hz, 2H), 7.52 (t, $J$=7.56 Hz, 2H), 5.55 (dd, $J$=2.80 Hz, 7.19 Hz, 4H), 4.65 (m, 1H) 1.67 (m, 1H), 1.56 (m, 1H), 1.41–1.23 (m, 19H), 0.88 (t, $J$=6.80 Hz, 3H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 146.4, 134.1 (d, $J$=2.3 Hz), 132.5 (d, $J$=8.4 Hz), 128.7 (d, $J$=2.3 Hz), 128.1 (d, $J$=5.3 Hz), 124.9, 77.6 (d, $J$=6.0 Hz), 65.8, 65.8, 65.7, 37.3 (d, $J$=6.0 Hz), 31.8, 29.5, 29.5, 29.4, 29.3, 29.2, 25.1, 22.6, 21.6, (d, $J$=3.1 Hz) 14.1; $^{31}$P NMR ($CDCl_3$, 162 MHz) $\delta$ −1.1; IR (film, $cm^{-1}$) 2924, 2854, 1614, 1579, 1524, 1448, 1340, 1271; TLC $R_f$ 0.46 (50% ethyl ether/toluene); Exact mass calcd for $[C_{26}H_{37}N_2O_8P+H]^+$ requires $m/z$ 537.2366. Found 537.2399 (FAB).

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## Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2012.08.070.

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