Cs$_2$CO$_3$-Mediated synthetic strategy for iprobenfos derivatives via thiophilic addition of H-phosphonates on in situ generated thioaldehydes

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This article is dedicated to Prof. Tien-Yau Luh on the occasion of his 76th birthday

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Abstract

The cesium carbonate-mediated synthetic approach for the synthesis of thiophosphates derivatives under mild conditions is reported. A variety of H-phosphonate successfully reacted with trithiaphosphinane sulfide derivatives possessing EWGs and EDGs. This method provides the synthetic platform for a broad spectrum of aryl sulfur surrogate to afford the desired products in 30-70% yields. In addition to practical utility, this protocol is feasible for the straightforward one-step synthesis of value-added agrochemical Iprobenfos derivatives in good yields.

Keywords: Thiophilic addition; iprobenfos derivatives; phosphorothioates
Introduction

Phosphorothioates having the phosphorus-sulfur bond are among the important scaffolds that exist in many bioactive molecules, drugs, and functional materials. The pharmaceutically privileged molecules containing the phosphorothioates skeleton exhibit significant biological activities such as anti-viral, anti-bacterial, anti-cancer agents, anti-fungal, and anti-inflammatory.\(^1\)-\(^3\) Phosphorothioates molecules such as demeton-S are used as insecticides whereas omethoate is used in the agrochemical industry.\(^4\)-\(^6\) Phosphorothioate molecule echothiopate (AChE inhibitor) is used in cardioprotective therapeutics (Figure 1).\(^7\)-\(^8\) Furthermore, phosphorothioates are also used as a key intermediate for synthesizing value-added complex molecules.\(^9\)-\(^10\) Therefore, the chemistry of phosphorus-sulfur compounds has become an interesting area of research for the scientific community. The related preceding research work such as the nucleophilic substitution reaction of dialkyl chlorophosphate with thiols, disulfides or sulfonyl halides and the Michaelis-Arbuzov-type reaction have been associated with some drawbacks and limitations such as the requirement of high temperature, and of hazardous and moisture-sensitive sulfur reagents, as well as with environmental pollution.\(^11\)-\(^17\)

Numerous organic sulfide surrogates which either not easily available or in unpleasant nature as disulfides, sulfonyl chlorides, sulfonyl hydrazides, and sulfenyl cyanides have been employed as coupling partners in the phosphorothiolation processes (Scheme 1a).\(^18\)-\(^23\) Tang and co-workers reported a Cu-catalyzed multicomponent reaction (MCR) using aryl boronic acids, elemental sulfur, and P(O)H compounds.\(^24\) Later on, the Tang group successfully achieved direct C(sp\(^2\))-H and C(sp\(^3\))-H phosphorothiolation via a multi-component composition strategy as shown in Scheme 1b.\(^25\)-\(^26\) The development of phosphorothiolic acids, phosphorothiolate salts, O, O-dialkyl-S-(N-phthalimido)-phosphorothioate, and dialkyl (2-cyanoethyl)-phosphonate has been achieved by phosphorothiolation process employing with alkyl halides, arylboronic acids, and arenediazonium salts, etc (Scheme 1c).\(^27\)-\(^30\) Despite the significant value of these methods for S-alkyl thiophosphates, the mostly substrates are pre-synthesized organic sulfides. Hence, a sustainable synthetic procedure which easily feasible with simple readily available and low-toxic reagents is still a desired place of research for phosphorothiolation reactions. Herein, we report a base-mediated novel, regioselective, and efficient synthetic approach for the synthesis of iprobenfos derivatives under mild reaction conditions (Scheme 1d).
Results and Discussion

To achieve the base-catalyzed P-S bond formation strategy, we chose trithiaposphinane sulfide derivative 1a and diethyl phosphites (2a) as model substrates. Initially, a reaction was carried out with the substrate 1a and 2a in the presence of potassium carbonate (40 mol %) in ethyl acetate at 80 °C for 10 hours under nitrogen atmosphere. Fascinatingly, the desired product 3a was obtained in 25% yield (Table 1, entry 1). To further optimize the reaction conditions, we screened a variety of bases and specifically K$_2$CO$_3$, NEt$_3$, DBU, CsF, tBuOK, NaOH, pyridine, and Cs$_2$CO$_3$. Among them, Cs$_2$CO$_3$ was found to be the most effective base that provided the compound 3a in 65% yield (entries 2-8). Subsequently, solvent systems such as ethanol (EtOH), dimethyl sulfoxide (DMSO), 1,4-dioxane, N,N-dimethylformamide (DMF), tetrahydrofuran (THF), and 1,2-dichloroethane (DCE) were screened. However, none of them was found to be superior to ethyl acetate (entries 9-14). A detrimental impact was observed on increasing the reaction temperature up to 100 °C (entry 15). Lower yields of 3a were observed, in reducing and prolonging the reaction time (entries 16-18). Based on the above discussed results, Cs$_2$CO$_3$ (40 mol %), and ethyl acetate at 80 °C for 10 hours were identified as the optimal reaction conditions that gave the optimal yield of 65% of 3a (entry 8).
Table 1. Optimization of the Reaction conditions

![Chemical Structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Solvent (2 mL)</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (3a)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>K₂CO₃</td>
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<td>10</td>
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<tr>
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<td>15</td>
</tr>
<tr>
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<tr>
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<td>CsF</td>
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<td>10</td>
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<td>80</td>
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<td>65</td>
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<tr>
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<td>80</td>
<td>10</td>
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<tr>
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<tr>
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<td>EA</td>
<td>80</td>
<td>24</td>
<td>39</td>
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</table>

*Reaction conditions: 1a (0.6 mmol), diethyl phosphite 2a (0.4 mmol), and base (40 mol %), under N₂ atmosphere at 80-100 °C heated for 8-24 h. Isolated yield based on 2a.*

Subsequently, the generality of the developed P-S bond formation protocol was examined, and the results are summarized in Table 2. The diverse variety of sulfur surrogates 1a-k possessing EDGs and EWGs were successfully reacted with diethyl phosphite (2a) under the optimized reaction conditions. Sulfur surrogates having EDGs (3-Me/4-OMe) reacted successfully with diethyl phosphite (2a) to afford the phosphorothioates 3b-f in 35-61% yields. Sulfur surrogates having EWGs (4-F, 4-Cl, 3-Br, 4-Br, and 4-I) also reacted with diethyl phosphite (2a) to afford the phosphorothioates 3g-k in 30-50% yields. Furthermore, naphthyl moiety containing sulfur surrogate 1l and heterocyclic thiophene containing sulfur surrogates 1m reacted with diethyl phosphite (2a) to lead to phosphorothioates 3l and 3m in 60% and 42% yield, respectively. The reactivity of di-i-butyl phosphite (2b) with various sulfur surrogates 1a-e which possess EDGs (2-Me, 3-Me, 3-OMe and 4-OMe) and EWGs (4-F, 4-Cl, 3-Br, 4-Br, 4-I, 4-NO₂) has been investigated. Thus, the phosphorothioates 3n-y were successfully synthesized in 30-70% yields. 2-Naphthyl 1l and 2-thienyl sulfur surrogate 1m, were also reacted with di-i-butyl phosphite (2b) and afforded the phosphorothioates 3z and 3aa in yield 61% and 42% respectively. The structures of compounds 3a-3z and 3aa were confirmed through characterization techniques including ¹H NMR, ¹³C NMR, ³¹P NMR, and HRMS data collection. Notably, we performed a large-scale reaction (5.0 mmol) using substrate 1a, which yielded the desired product 3a with 60% (Scheme 2).
Table 2. Substrate scope\textsuperscript{a,b}

\[
\begin{array}{cccc}
\text{Ar} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} + \text{R} & \text{O} & \text{P} & \text{H} \\
\hline
\text{3a} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3b} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3c} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3d} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3e} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3f} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3g} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3h} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3i} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3j} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3k} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3l} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3m} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3n} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3o} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3p} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3q} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3r} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3s} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3t} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3u} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3v} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3w} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3x} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3y} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3z} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\text{3aa} & \text{EtO} & \text{O} & \text{Et} & \text{S} & \text{S} & \text{S} & \text{P} & \text{O} & \text{Me} & \text{R} & \text{O} & \text{P} & \text{H} \\
\end{array}
\]

\textsuperscript{a}Reaction conditions: 1 (0.6 mmol), phosphites 2 (0.4 mmol), Cs\textsubscript{2}CO\textsubscript{3} (40 mol\%), and ethyl acetate (2 mL) under N\textsubscript{2} at 80 °C for 10 h. \textsuperscript{b}Isolated yields based on 2.

Scheme 2. Gram scale synthesis.

Based on the previous reports\textsuperscript{31-36} and our experimental observations, we propose a mechanistic pathway illustrated in Scheme 3. Initially, phosphite 2 interacts with Cs\textsubscript{2}CO\textsubscript{3} and transforms into cesium-stabilized phosphate anion I. Trithiaphosphinane sulfides 1 in the presence of Cs\textsubscript{2}CO\textsubscript{3} in-situ generated thialdehyde 1’. 
Later on I reacted with thialdehyde I' through thiophilic addition to provide intermediate species II which upon protonation with another molecule phosphite 2 provided the resulting thiophosphates 3.

Scheme 3. Plausible reaction mechanism.

Conclusions

This protocol developed provides the Cs₂CO₃-catalytic synthetic strategy for the synthesis of thiophosphates via a thiophilic addition of H-phosphites on in-situ generated thialdehydes. A wide variety of sulfur surrogates were well tolerated under these conditions and provided a good library of thiophosphates compounds. The developed protocol exhibits remarkable functional group tolerance, and the reactivity pattern was dependent on the substituents that attached the moieties. The gram scale synthesis, base-catalysis, and mild conditions are the main feature of this developed protocol which proves the effectiveness of this protocol.

Experimental Section

General: Reagents, substrates, and solvents were purchased from commercial suppliers and used without purification. Anhydrous toluene uses calcium hydride to remove water, dry, and distill. Analytical thin-layer chromatography (TLC) was performed using silica gel 60 F₂₅₄ (Merck). Chromatography was performed using silica gel 60 (43-63 um) (Merck) and Aluminum oxide 90 neutral (MN). ¹H, ¹³C, ³¹P, and ¹⁹F NMR spectra were using CDCl₃ on Jeol 400 MHz spectrometers. Tetramethylsilane (TMS) served as an internal standard for ¹H and ¹³C NMR analysis. Chemical shifts in ¹H NMR and ¹³C NMR spectra are reported as follows: Chloroform-d (referenced to 7.26 ppm for ¹H and 77.10 ppm for ¹³C). Coupling constants (J) are reported in hertz and peak multiplicities are reported using the following abbreviations: m = multiplet; s = singlet; d = doublet; t = triplet; q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, td = triplet of doublets, tq = triplet of quartets, qd = quartet of doublets, br = broad signal. Low-Resolution Mass Spectrometry (LRMS) experiments were recorded on an Agilent Technologies 5977A with Agilent Technologies 7890B. High-Resolution Mass Spectrometry (HRMS) experiments were recorded on Jeol JMS-HX-110 with EI (Electron Impact)
method. All the phosphites 2a & 2b commercially purchased and used without purification and all the thioaldehydes 1a-m were prepared from known literature methods.37

**General procedure for Table 1.** In a sealed tube, 2-(4-methoxyphenyl)-4,6-diphenyl-1,3,5,2-trithiapinophanane 2-sulfide (1a) (267.9 mg, 0.6 mmol), base (40 mol %) was added in a glove box, followed by diethyl phosphites 2a (55.24 mg, 0.4 mmol) and solvent (2 mL) were added, and stir at 80-100 °C for 8-10 hours. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered through a celite pad and concentrated under reduced pressure. The crude product thus obtained was then purified by column chromatography using silica gel (300-400 mesh) (15% ethyl acetate in hexanes) to obtain the pure product of 3a.

**Representative example of Table 1. S-Benzyl O,O-diisobutyl phosphorothioate (3a).**38 Yield: 77.66 mg, 65%; 1H NMR (400 MHz, CDCl3): δ 7.37-7.24 (m, 5H), 4.16-3.96 (m, 6H), 1.28 (t, J 7.2 Hz, 6H); 13C{H}NMR (100 MHz, CDCl3): δ 137.4 (d, J 6.0 Hz), 128.9, 128.6, 127.6, 63.5 (d, J 6.0 Hz), 34.9 (d, J 3.0 Hz), 15.9 (d, J 7.0 Hz); 31P NMR (162 MHz, CDCl3): δ 27.3.

**General procedure for Table 2.** In a sealed tube, added 1 (0.6 mmol), cesium carbonate (40 mol %) in a glove box, then dialkyl phosphites 2 (0.4 mmol) and ethyl acetate (2 mL) were added, the reaction mixture was then heated for 10 hours at 80 °C. After completion of the reaction, the reaction mixture was diluted with ethyl acetate and filtered through a celite pad and concentrated under reduced pressure. The crude product thus obtained was purified by column chromatography using silica gel (300-400 mesh) (10-20% ethyl acetate in hexanes) to obtain the pure products 3.

**O,O-Diethyl S-(3-methylbenzyl) phosphorothioate (3b).**39 The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di-m-tolyl-1,3,5,2-trithiapinophanane 2-sulfide (1b) (284.7 mg, 0.6 mmol), diethyl phosphite (2a) (55.24 mg, 0.4 mmol), Cs2CO3 (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO2, ethyl acetate/hexane) to provide 3b (66.92 mg, 61% yield); 1H NMR (400 MHz, CDCl3): δ 7.27-7.14 (m, 3H), 7.08 (d, J 7.2 Hz, 1H), 4.18-3.98 (m, 6H), 2.34 (s, 3H), 1.29 (t, J=7.2 Hz, 6H); 13C{H}NMR (100 MHz, CDCl3): δ 138.2, 137.3 (d, J 6.0 Hz), 129.6, 128.6, 128.4, 125.9, 63.5 (d, J 5.0 Hz), 34.9 (d, J 4.0 Hz), 21.3, 15.9 (d, J 8.0 Hz); 31P NMR (162 MHz, CDCl3): δ 27.4. HRMS (EI) calcd for C12H19O3PS [M]+ 274.0793 found: 274.0784.

**O,O-Diethyl S-(2-methylbenzyl) phosphorothioate (3c).**39 The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di-o-tolyl-1,3,5,2-trithiapinophanane 2-sulfide (1c) (284.7 mg, 0.6 mmol), diethyl phosphite 2a (55.24 mg, 0.4 mmol), Cs2CO3 (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO2, ethyl acetate/hexane) to provide 3c (65.82 mg, 60% yield); 1H NMR (400 MHz, CDCl3): δ 7.31 (d, J 6.8 Hz, 1H), 7.21-7.13 (m, 3H), 4.18-3.99 (m, 6H), 2.40 (s, 3H), 1.30 (td, J 7.2 & 0.8 Hz, 6H); 13C{H}NMR (100 MHz, CDCl3): δ 136.6, 135.1 (d, J 6.0 Hz), 130.6, 130.0, 128.1, 126.2, 63.5 (d, J 6.0 Hz), 33.1 (d, J 3.0 Hz), 19.2, 16.0 (d, J 8.0 Hz); 31P NMR (162 MHz, CDCl3): δ 27.4.

**O,O-Diethyl S-(4-methylbenzyl) phosphorothioate (3d).**39 The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di-p-tolyl-1,3,5,2-trithiapinophanane 2-sulfide (1d) (284.7 mg, 0.6 mmol), diethyl phosphite (2a) (55.24 mg, 0.4 mmol), Cs2CO3 (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO2, ethyl acetate/hexane) to provide 3d as a colorless liquid (66.92 mg, 61% yield); 1H NMR (400 MHz, CDCl3): δ 7.23 (d, J 8.0 Hz, 2H), 7.20 (d, J 8.0 Hz, 2H), 4.73-3.98 (m, 6H), 2.32 (s, 3H), 1.29 (t, J 7.2 Hz, 6H); 13C{H}NMR (100 MHz, CDCl3) δ 137.2, 134.2 (d, J 6.0 Hz), 129.2, 128.7, 63.4 (d, J 5.0 Hz), 34.6 (d, J 4.0 Hz), 21.0 (s), 15.8 (d, J 7.0 Hz); 31P NMR (162 MHz, CDCl3) δ 27.5. HRMS (EI) calcd for C12H19O3PS [M]+ 274.0793 found: 274.0784.
**O,O-Diethyl S-(3-methoxybenzyl) phosphorothioate (3e).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-methoxyphenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiapophosphinane 2-sulfide (1e) (304.0 mg, 0.6 mmol), diethyl phosphate 2a (55.24 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3e as a colorless liquid (40.60 mg, 35% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (t, J 8.0 Hz, 1H), 6.95-6.90 (m, 2H), 6.80 (dd, J 8.4 & 2.4 Hz, 1H), 4.17-3.98 (m, 6H), 3.80 (s, 3H), 1.29 (t, J 7.2 Hz, 6H); ¹³C(H)NMR (100 MHz, CDCl₃): δ 159.6, 138.9 (d, 6.0 Hz), 129.6, 121.0, 114.3, 113.2, 63.4 (d, J 6.0 Hz), 55.1, 34.8 (d, J 4.0 Hz), 15.8 (d, J 8.0 Hz); ³¹P NMR (162 MHz, CDCl₃): δ 27.3. HRMS (EI) calcd for C₁₂H₁₀O₄ PS [M⁺] 290.0742 found: 290.0743.

**O,O-Diethyl S-(4-fluorobenzyl) phosphorothioate (3f).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-methoxyphenyl)-1,3,5,2-trithiapophosphinane 2-sulfide (1f) (304.0 mg, 0.6 mmol), diethyl phosphate 2a (55.24 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3f (55.65 mg, 49% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.27 (d, J 8.8 Hz, 2H), 6.84 (d, J 8.8 Hz, 2H), 4.17-3.98 (m, 6H), 3.79 (s, 3H), 1.29 (t, J 7.2 Hz, 6H); ¹³C(H)NMR (100 MHz, CDCl₃): δ 159.0, 130.1, 129.4 (d, J 6.0 Hz), 114.0, 63.4 (d, J 6.0 Hz), 55.3, 34.5 (d, J 4.0 Hz), 15.9 (d, J 8.0 Hz); ³¹P NMR (162 MHz, CDCl₃): δ 27.5.

**S-(4-Chlorobenzyl) O,O-diethyl phosphorothioate (3g).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(4-fluorophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiapophosphinane 2-sulfide (1g) (289.4 mg, 0.6 mmol), diethyl phosphate 2a (55.24 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3g (52.13 mg, 40 mol % yield); ¹H NMR (400 MHz, CDCl₃): δ 7.35-7.31 (m, 2H), 7.03-6.97 (m, 2H), 4.16-3.97 (m, 6H), 1.29 (td, J 7.2 & 0.8 Hz, 6H); ¹³C(H)NMR (100 MHz, CDCl₃): δ 162.2 (d, J 236.0 Hz), 133.4 (dd, J 4.0 & 5.0 Hz), 130.4 (d, J 9.0 Hz), 115.4 (d, J 21.0 Hz), 63.5 (d, J 6.0 Hz), 34.1 (d, J 3.0 Hz), 15.8 (d, J 7.0 Hz); ³¹P NMR (162 MHz, CDCl₃): δ 27.1; ¹⁹F NMR (376 MHz, CDCl₃): δ -114.5. HRMS (EI) calcd for C₁₁H₁₆F₂O₂PS [M⁺] 278.0542 found: 278.0544.

**S-(3-Methoxyphenyl) O,O-diethyl phosphorothioate (3i).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-methoxyphenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiapophosphinane 2-sulfide (1i) (309.2 mg, 0.6 mmol), diethyl phosphate 2a (55.24 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3i (35.28 mg, 30% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.27 (m, 4H), 4.16-3.97 (m, 6H), 1.29 (td, J 3.2 & 0.8 Hz, 6H); ¹³C(H)NMR (100 MHz, CDCl₃): δ 136.2 (d, J 5.0 Hz), 133.5, 130.3, 128.8, 63.6 (d, J 5.0 Hz), 34.2 (d, J 3.9 Hz), 15.9 (d, J 7.0 Hz); ³¹P NMR (162 MHz, CDCl₃): δ 27.0. HRMS (EI) calcd for C₁₁H₁₄Cl₂O₂PS [M⁺] 294.0246 found: 294.0238.

**S-(3-Bromobenzyl) O,O-diethyl phosphorothioate (3j).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-bromophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiapophosphinane 2-sulfide (1j) (362.6 mg, 0.6 mmol), diethyl phosphate 2a (55.24 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3j (35.05 mg, 45% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.43 (m, 2H), 7.27-7.22 (m, 2H), 4.16-3.96 (m, 6H), 1.28 (td, J 7.2 & 0.8 Hz, 6H); ¹¹C(H)NMR (100 MHz, CDCl₃): δ 136.6 (d, J 5.0 Hz), 131.7, 130.6, 121.5, 63.6 (d, J 6.0 Hz), 34.2 (d,
J 4.0 Hz), 15.9 (d, J 7.0 Hz); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)): \(\delta\) 26.9. HRMS (El) calcd for C\(_{11}\)H\(_{16}\)Br\(_3\)O\(_3\)PS [M\(^+\)] 337.9741 found: 337.9739.

**O,O-Diethyl S-(4-iodobenzyl) phosphorothioate (3k).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(4-iodophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaporphinane 2-sulfide (1k) (419.0 mg, 0.6 mmol), diethyl phosphate (2a) (55.24 mg, 0.4 mmol), Cs\(_2\)CO\(_3\) (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO\(_2\), ethyl acetate/hexane) to provide 3k (72.6 mg, 50% yield); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.64 (d, J 8.4 Hz, 2H), 7.12 (d, J 8.4 Hz, 2H), 4.15-3.94 (m, 6H), 1.28 (td, J 7.2 & 0.8 Hz, 6H); \(^{13}\)C(H)NMR (100 MHz, CDCl\(_3\)): \(\delta\) 137.6, 137.2 (d, J 5.0 Hz), 130.7, 93.0, 63.5 (d, J 6.0 Hz), 34.2, 15.8 (d, J 8.0 Hz); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)) 26.8; HRMS (El) calcd for C\(_{13}\)H\(_{18}\)O\(_3\)PS [M\(^+\)] 385.9602 found: 385.9599.

**O,O-Diethyl S-(naphthalen-2-ylmethyl) phosphorothioate (3l).** The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di(naphthalen-2-yl)-1,3,5,2-trithiaporphinane 2-sulfide (1l) (328.0 mg, 0.6 mmol), diethyl phosphate (2a) (55.24 mg, 0.4 mmol), Cs\(_2\)CO\(_3\) (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO\(_2\), ethyl acetate/hexane) to provide 3l (55.24 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO\(_2\), ethyl acetate/hexane) to provide 3l (77.68 mg, 0.4 mmol), Cs\(_2\)CO\(_3\) (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO\(_2\), ethyl acetate/hexane) to provide 3l (88.58 mg, 70% yield); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39 (dd, J 8.0 Hz, 1H), 6.93-6.90 (m, 1H), 4.27 (d, J 14.0 Hz, 2H), 4.20-4.01 (m, 4H), 1.31 (t, J 7.2 Hz, 6H); \(^{13}\)C(H)NMR (100 MHz, CDCl\(_3\)): \(\delta\) 140.0 (d, J 6.0 Hz), 127.1, 126.9, 125.7, 63.6 (d, J 5.0 Hz), 29.5 (d, J 3.0 Hz), 15.9 (d, J 7.0 Hz); \(^{31}\)P NMR (162 MHz, CDCl\(_3\)): \(\delta\) 26.7. HRMS (El) calcd for C\(_{26}\)H\(_{35}\)O\(_3\)PS [M\(^+\)] 310.0793 found: 310.0789.

**S-Benzyl O,O-diisobutyl phosphorothioate (3n).** The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di(p-tolyl)-1,3,5,2-trithiaporphinane 2-sulfide (1a) (267.9 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs\(_2\)CO\(_3\) (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO\(_2\), ethyl acetate/hexane) to provide 3n (88.58 mg, 70% yield); \(^{1}\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.39-7.24 (m, 5H), 4.04 (d, J 14.0 Hz, 2H), 3.84-3.78 (m, 2H), 3.73-3.67 (m, 2H), 1.95-1.85 (m, 2H), 0.92 (d, J 1.2 Hz, 6H), 0.90 (d, J 1.2 Hz, 6H), \(^{13}\)C(H)NMR (100 MHz, CDCl\(_3\)): \(\delta\) 137.5 (d, J 5.0 Hz), 128.9, 128.7, 127.6, 73.3 (d, J 7.0 Hz), 34.9 (d, J 3.0 Hz), 28.9 (d, J 8.0 Hz), 18.7; \(^{31}\)P NMR (162 MHz, CDCl\(_3\)): \(\delta\) 27.4.
(1b) (284.7 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (53.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3p (76.65 mg, 58% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (t, J 8.0 Hz, 1H), 6.94 (d, J 7.6 Hz, 1H), 6.91 (t, J 2.0 Hz, 1H), 6.81 (dd, J 8.4 & 2.4 Hz, 1H), 4.02 (d, J 13.6 Hz, 2H), 3.85-3.79 (m, 5H), 3.75-3.69 (m, 2H), 1.96-1.86 (m, 2H), 0.93 (d, J 1.2 Hz, 6H), 0.91 (d, J 1.2 Hz, 6H). ¹³C(H) NMR (100 MHz, CDCl₃): δ 159.7, 139.0 (d, J 5.0 Hz), 129.7, 121.2, 114.4, 113.3, 73.4 (d, J 6.0 Hz), 55.3, 34.9, (d, J 4.0 Hz), 29.0 (d, J 7.0 Hz), 18.7. ³¹P NMR (162 MHz, CDCl₃): δ 27.4. HRMS (EI) calcd for C₁₅H₂₂O₃PS [M]+ 330.1419 found: 330.1422.

**O,O-Diisobutyl S-(2-methylbenzyl) phosphorothioate (3q).** The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di-o-toly1-1,3,5,2-trithiaphosphinane 2-sulfide (1c) (284.7 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3q (79.30 mg, 60% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.30 (m, 1H), 7.20-7.12 (m, 3H), 4.06 (d, J 12.0 Hz, 2H), 3.85-3.80 (m, 2H), 3.75-3.70 (m, 2H), 2.40 (s, 3H), 1.97-1.87 (m, 2H), 0.93 (d, J 1.2 Hz, 6H), 0.91 (d, J 1.2 Hz, 6H); ¹³C(H) NMR (100 MHz, CDCl₃): δ 136.6, 135.1 (d, J 6.0 Hz), 130.5, 129.9, 128.0, 126.2, 73.3 (d, J 7.0 Hz), 33.0 (d, J 3.0 Hz), 28.9 (d, J 7.0 Hz), 19.1, 18.6. ³¹P NMR (162 MHz, CDCl₃): δ 27.5. HRMS (EI) calcd for C₁₆H₂₃O₃PS [M]+ 330.1419 found: 330.1416.

**O,O-Diisobutyl S-(3-methoxybenzyl) phosphorothioate (3r).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-methoxyphenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-sulfide (1e) (304.0 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3r (66.50 mg, 48% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.23 (t, J 8.0 Hz, 1H), 6.95-6.91 (m, 2H), 6.80 (dd, J 8.0 & 2.0 Hz, 1H), 4.02 (d, J 14.0 Hz, 2H), 3.83-3.79 (m, 5H), 3.75-3.71 (m, 2H), 1.96-1.86 (m, 2H), 0.92 (d, J 1.2 Hz, 6H), 0.91 (d, J 1.2 Hz, 6H); ¹³C(H) NMR (100 MHz, CDCl₃): δ 159.7, 138.9 (d, J 6.0 Hz), 129.7, 121.2, 114.3, 113.2, 73.3 (d, J 6.0 Hz), 55.2, 34.8 (d, J 4.0 Hz), 28.9 (d, J 7.0 Hz), 18.7. ³¹P NMR (162 MHz, CDCl₃): δ 27.4. HRMS (EI) calcd for C₁₆H₂₄O₃PS [M]+ 346.1368 found: 346.1363.

**O,O-Diisobutyl S-(4-methoxybenzyl) phosphorothioate (3s).** The title compound was prepared following the general procedure for table 2, using 2,4,6-tris(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-sulfide (1f) (304.0 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3s (88.67 mg, 64% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.30-7.26 (m, 2H), 6.87-6.82 (m, 2H), 4.02 (d, J 13.2 Hz, 2H), 3.84-3.78 (m, 5H), 3.74-3.68 (m, 2H), 1.96-1.87 (m, 3H), 0.93 (d, J 3.0 Hz, 6H), 0.91 (d, J 3.0 Hz, 6H); ¹³C(H) NMR (100 MHz, CDCl₃): δ 159.0, 130.1, 129.4 (d, J 5.0 Hz), 114.4, 73.3 (d, J 7.0 Hz), 55.3 (s), 34.5 (d, J 4.0 Hz), 28.9 (d, J 8.0 Hz), 18.6. ³¹P NMR (162 MHz, CDCl₃): δ 27.6. HRMS (EI) calcd for C₁₆H₂₄O₃PS [M]+ 346.1368 found: 346.1363.

**S-(4-Fluorobenzyl) O,O-diisobutyl phosphorothioate (3t).** The title compound was prepared following the general procedure for table 2 using 4,6-bis(4-fluorophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-sulfide (1g) (289.4 mg, 0.6 mmol), di-isobutyl phosphate (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3t (77.57 mg, 58% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.36-7.32 (m, 2H), 7.03-6.98 (m, 2H), 4.03 (d, J 14.0 Hz, 2H), 3.84-3.78 (m, 2H), 3.74-3.68 (m, 2H), 1.95-1.87 (m, 2H), 0.92 (d, J 6.8 Hz, 12H); ¹³C(H) NMR (100 MHz, CDCl₃): δ 161.6 (d, J 170.0 Hz), 133.2 (d, J 125.0 Hz), 130.4 (d, J 9.0 Hz), 115.6 (d, J 21.0 Hz), 73.4 (d, J 7.0 Hz), 34.2 (d, J 4.0 Hz), 29.0 (d, J 7.0 Hz), 18.7; ³¹P NMR (162 MHz, CDCl₃): δ 27.1; ¹⁹F NMR (376 MHz, CDCl₃): δ -114.5. HRMS (EI) calcd for C₁₅H₂₄F₂O₃PS [M]+ 334.1168 found: 334.1172.

**S-(4-Chlorobenzyl) O,O-diisobutyl phosphorothioate (3u).** The title compound was prepared following the general procedure for table 2, using 4,6-bis(4-chlorophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-
sulfide (1h) (309.2 mg, 0.6 mmol), di-isobutyl phosphite (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3u (70.16 mg, 50% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.32-7.27 (m, 4H), 4.01 (d, J 14.4 Hz, 2H), 3.83-3.77 (m, 2H), 3.73-3.67 (m, 2H), 1.95-1.85 (m, 2H), 0.91 (d, J 6.8 Hz, 12H); ¹³C{H}NMR (100 MHz, CDCl₃): δ 136.2 (d, J 5.0 Hz), 133.4, 130.3, 128.8, 73.4 (d, J 7.0 Hz), 34.2 (d, J 4.0 Hz), 28.9 (d, J 7.0 Hz), 18.6. ³¹P NMR (162 MHz, CDCl₃): δ 27.0. HRMS (EI) calc for C₁₅H₂₄ClO₃PS [M⁺]: 350.0872 found: 350.0869.

S-(3-Bromobenzyl) O,O-diisobutyl phosphorothioate (3v). The title compound was prepared following the general procedure for table 2, using 4,6-bis(3-bromophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-sulfide (1i) (362.6 mg, 0.6 mmol), di-isobutyl phosphite (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3v (102.77 mg, 65% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.52 (t, J 1.6 Hz, 1H), 7.40-7.37 (m, 1H), 7.31-7.27 (m, 1H), 7.19 (t, J 8.0 Hz, 1H), 3.98 (d, J 14.8 Hz, 2H), 3.84-3.79 (m, 2H), 3.74-3.67 (m, 2H), 1.95-1.85 (m, 2H), 0.92 (d, J 0.8 Hz, 6H), 0.90 (d, J 1.2 Hz, 6H); ¹³C{H} NMR (100 MHz, CDCl₃): δ 134.0 (d, J 5.0 Hz), 125.8, 124.6, 124.1, 121.5, 116.4, 67.3 (d, J 7.0 Hz), 28.1, 22.8 (d, J= 8.0 Hz), 12.6; ³¹P NMR (162 MHz, CDCl₃): δ 26.85. HRMS (EI) calc for C₁₅H₂₄BrO₃PS [M⁺]: 394.0367 found: 394.0358.

S-(4-Bromobenzyl) O,O-diisobutyl phosphorothioate (3w). The title compound was prepared following the general procedure for table 2, using 4,6-bis(4-bromophenyl)-2-(4-methoxyphenyl)-1,3,5,2-trithiaphosphinane 2-sulfide (1j) (362.6 mg, 0.6 mmol), di-isobutyl phosphite (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3w (109.10 mg, 69% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.46-7.43 (m, 2H), 7.26-7.23 (m, 2H), 3.99 (d, J 14.8 Hz, 2H), 3.83-3.77 (m, 2H), 3.73-3.67 (m, 2H), 1.95-1.85 (m, 2H), 0.91 (d, J 6.8 Hz, 12H); ¹³C{H}NMR (100 MHz, CDCl₃): δ 136.7 (d, J 5.0 Hz), 131.7, 130.6, 121.5, 73.4 (d, J 6.0 Hz), 34.2 (d, J 4.0 Hz), 28.8 (d, J 8.0 Hz), 18.6. ³¹P NMR (162 MHz, CDCl₃): δ 26.9. HRMS (EI) calc for C₁₇H₂₄BrO₃PS [M⁺]: 412.0287 found: 412.0234.

S-(4-Iodobenzyl) O,O-diisobutyl phosphorothioate (3x). The title compound was prepared following the general procedure for table 2, using 4-iodobenzothioaldehyde 1k (148.8 mg, 0.6 mmol), di-isobutyl phosphite 2b (419.0 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3x (72.53 mg, 41% yield); ¹H NMR (400 MHz, CDCl₃): δ 7.64 (dt, J 8.8 & 2.4 Hz, 2H), 7.12 (dt, J 8.8 & 2.4 Hz, 2H), 3.98 (d, J 14.8 Hz, 2H), 3.82-3.77 (m, 2H), 3.72-3.66 (m, 2H), 1.94-1.84 (m, 2H), 0.91 (d, J 0.8 Hz, 6H), 0.90 (d, J 0.8 Hz, 6H); ¹³C{H}NMR (100 MHz, CDCl₃): δ 137.7, 137.5 (d, J 5.0 Hz), 130.9, 93.0, 73.4 (d, J 7.0 Hz), 34.4 (d, J 4.0 Hz), 28.9 (d, J 8.0 Hz), 18.7; ³¹P NMR (162 MHz, CDCl₃): δ 26.9. HRMS (EI) calc for C₁₇H₂₄I₂O₃PS [M⁺]: 442.0228 found: 442.0234.

O,O-Diisobutyl S-(4-nitrobenzyl) phosphorothioate (3y). The title compound was prepared following the general procedure for table 2, using 4-nitrobenzothioaldehyde 1n (100.3 mg, 0.6 mmol), di-isobutyl phosphite 2b (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3y (43.36 mg, 30% yield); ¹H NMR (400 MHz, CDCl₃): δ 8.20-8.16 (m, 2H), 7.58-7.55 (m, 2H), 4.12 (d, J 15.6 Hz, 2H), 3.84-3.75 (m, 2H), 3.74-3.68 (m, 2H), 1.95-1.85 (m, 2H), 0.85 (d, J 6.9 Hz, 12H); ¹³C{H}NMR (100 MHz, CDCl₃): δ 147.2, 145.4 (d, J 4.0 Hz), 129.7, 123.8, 73.6 (d, J 7.0 Hz), 34.0 (d, J 4.0 Hz), 29.8 (d, J 7.0 Hz), 18.6; ³¹P NMR (162 MHz, CDCl₃): δ 26.2. HRMS (EI) calc for C₁₅H₂₄NO₃PS [M⁺]: 361.1113 found: 361.1117.

O,O-Diisobutyl S-(naphthalen-2-ylmethyl) phosphorothioate (3z). The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di(naphthalen-2-yl)-1,3,5,2-tritiaphosphinane 2-sulfide (1l) (328.0 mg, 0.6 mmol), di-isobutyl phosphite (2b) (77.68 mg, 0.4 mmol), Cs₂CO₃ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO₂, ethyl acetate/hexane) to provide 3z (89.41 mg, 61% yield); ¹H NMR (400 MHz, CDCl₃): δ 8.07 (d, J 8.4 Hz, 1H), 7.83 (d, J 8.0 Hz, 1H), 7.76
(d, J 8.0 Hz, 1H), 7.57-7.47 (m, 3H), 7.39-7.35 (m, 1H), 4.51 (d, J 12.4 Hz, 2H), 3.83-3.76 (m, 2H), 3.73-3.67 (m, 2H), 1.92-1.82 (m, 2H), 0.89 (d, J 4.0 Hz, 6H), 0.87 (d, J 4.0 Hz, 6H); $^{13}$C{H}NMR (100 MHz, CDCl$_3$) δ 133.7, 132.6 (d, J 6.0 Hz), 130.9, 128.77, 128.70, 127.6, 125.8, 125.2, 123.5, 73.2 (d, J 7.0 Hz), 32.6 (d, J 4.0 Hz), 28.7 (d, J 7.0 Hz), 18.5; $^{31}$P NMR (162 MHz, CDCl$_3$) δ 27.4. HRMS (EI) calcd for C$_{19}$H$_{27}$O$_3$PS [M]+ 366.1419 found: 366.1416.

**O,O-Diisobutyl S-(thiophen-2-ylmethyl) phosphorothioate (3aa).** The title compound was prepared following the general procedure for table 2, using 2-(4-methoxyphenyl)-4,6-di(thiophen-2-yl)-1,3,5,2-trithiapinane 2-sulfide (1m) (275.1 mg, 0.6 mmol), di-isobutyl phosphite (2b) (77.68 mg, 0.4 mmol), Cs$_2$CO$_3$ (52.13 mg, 40 mol %) and EA (2.0 mL), then purified by column chromatography (SiO$_2$, ethyl acetate/hexane) to provide 3aa (54.16 mg, 42% yield); $^1$H NMR (400 MHz, CDCl$_3$): δ 7.22 (dd, J 5.2 & 1.2 Hz, 1H), 7.03 (dd, J 3.6 & 1.2 Hz, 1H), 6.91 (dd, J 5.2 & 3.6 Hz, 1H), 4.28 (d, J 13.6 Hz, 2H), 3.88-3.82 (m, 2H), 3.78-3.72 (m, 2H), 1.99-1.88 (m, 2H), 0.93 (d, J 17.0 Hz, 12H); $^{13}$C{H}NMR (100 MHz, CDCl$_3$): δ 140.0 (d, J 6.0 Hz), 127.1, 126.8, 125.6, 73.3 (d, J 7.0 Hz), 29.4 (d, J 3.0 Hz), 28.9 (d, J 8.0 Hz), 18.6; $^{31}$P NMR (162 MHz, CDCl$_3$): δ 26.7. HRMS (EI) calcd for C$_{13}$H$_{23}$O$_3$PS$_2$ [M]+ 322.0826 found: 322.0819.

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### Supplementary Material

Experimental for the preparation of trithiapinanes 1a-n, and copies of $^1$H, $^{13}$C, $^{31}$P & $^{19}$F NMR spectra of compounds 1 & 3 are available in the supplementary material associated with this manuscript.

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