

## Supporting Information

### Framework towards more Sustainable Chemical Synthesis Design – A Case Study of Organophosphates

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This supporting information contains the items listed in the below table of contents including functional groups supported in this methodology, molecular descriptors for each functional group, and analysis of literature references to support generalization of organophosphate synthesis schemes.

20 Pages, 2 Figures and 9 Tables

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3. Description of green chemistry evaluation to arrive at the four general schemes



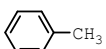

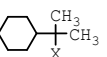




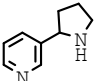

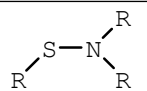




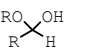






- a) **Figure S1:** Synthesis of triphenyl phosphates via catalysis
- b) **Figure S2:** Synthesis of triphenyl phosphate via oxidation of phosphites (Scheme B)




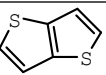
## Functional Groups

Functional groups are specific groups of atoms or bonds, within a molecule, that are responsible for the characteristics of a chemical. A chemical compound's functional group or groups can produce information such as the reactivity, solubility, stability and possible interaction with other functional groups. However, the fact that some chemicals can have two or more different type of functional groups renders these compounds more complex. By breaking down a molecule into its component functional groups, not only is functionality identified and organic chemical class identified, but also the potential to produce plausible green and sustainable synthesis routes.

Table S1 provides a listing and group of identified functional groups residing within the proposed framework. This table is organized to provide classification of function groups based on atoms present.

**Table S1.** Matrix of organic chemical functionality categorized by atoms within the functional group (e.g. C and H, C, N and H and C, N, O and H).

	CARBON	NITROGEN	OXYGEN	PHOSPHOROUS	SULFUR
CARBON	<div><div><math>R-R'</math> alkanes</div><div><math>R=R'</math> alkenes</div><div><math>R\equiv R'</math> alkynes</div><div><math>R-X</math> alkyl halide</div></div> <div><div> aromatic</div><div> arenes</div><div> toluene</div></div> <div><div> diene</div><div> haloalkane</div><div> cyclo alkane</div></div> <div><math>R = C, CH, CH_2, CH_3</math></div>				
NITROGEN		<div><div> pyridine</div><div> imidzole</div><div> amides</div></div> <div><div><math>R-N=N-R'</math> azo</div><div><math>N=N=N</math> azide</div><div> alkaloids</div></div> <div><div> amines</div><div><math>H_2N-NH_2</math> hydrazine</div></div>			<div> sulfenamide</div>
OXYGEN	<div><div><math>R-OH</math> alcohol</div><div><math>R-C(=O)OH</math> carboxyl</div><div> hydrofuran</div><div> furan</div></div> <div><div><math>R-O-R'</math> ether</div><div> phenol</div><div><math>HCO_2-R-CO_2H</math> dicarboxyl</div><div><math>-O-C(=O)-O-</math> carbonate</div></div> <div><div><math>R-C(=O)-R'</math> ketone</div><div> pyran</div><div><math>R-C(=O)-O-R</math> ester</div><div> orthoester</div></div> <div><div><math>R-CHO</math> aldehyde</div><div> epoxide</div><div><math>R-C(=O)-O-C(=O)-R^2</math> anhydride</div></div> <div><div> chroman</div><div><math>R_1-O-C(R_3)(R_4)-O-R_2</math> acetal</div><div><math>R^2-O-O-R^2</math> peroxide</div></div> <div><div><math>MeO-R</math> methoxy</div><div> orthocarbonic</div><div><math>R-C(=O)-C(=O)-R</math> ketene</div></div>	<div><div><math>R-C(=O)-N(R')R''</math> amides</div><div> azole</div><div><math>H_2N-OH</math> hydroxylamine</div></div> <div><div><math>H_2N-C(=O)-NH_2</math> semicarbazid</div><div> oxime</div><div><math>R-O-N=O</math> nitro</div></div> <div><div><math>O=C(R)-N(R')C(=O)R''</math> imide</div><div><math>-O=N=O-</math> nitrate</div><div><math>[O=N=O]</math> nitrite</div></div> <div><div><math>H_2N-CH(R)-COOH</math> amino acid</div><div> isoxazole</div><div><math>HN=C=O</math> cyanates</div></div>	<div><math>H-O-O-H</math> peroxide</div>	<div><div><math>O=S(=O)(OH)O^-</math> sulfate</div><div><math>R-S(=O)(=O)O^-</math> sulfonate ester</div><div><math>R-S(=O)(=O)R</math> sulfones</div><div><math>R-S(=O)R</math> sulfoxide</div></div>	

<b>PHOSPHOROUS</b>	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} R_1 \\   \\ R_2 \diagup P - R_3 \\   \\ R_4 \diagdown \\   \\ R_5 \end{array}</math> <p>phosphorane</p> </div> <div style="text-align: center;">  <p>phosphorine</p> </div> </div>	<div style="text-align: center;"> <math display="block">R-P=N \\   \\ R</math> <p>phosphazene</p> </div>	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="display: flex; justify-content: space-around; width: 100%;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} HO \\   \\ HO-CH_2-P^+(OH)_2 \\   \\ OH \end{array}</math> <p>phosphonium</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O^- \\   \\ -O-P-O^- \end{array}</math> <p>phosphite</p> </div> </div> <div style="display: flex; justify-content: space-around; width: 100%;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ -O-P-O^- \\   \\ O^- \end{array}</math> <p>phosphate</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ -O-P-OR \\   \\ OR \end{array}</math> <p>phosphodiester</p> </div> </div> <div style="display: flex; justify-content: space-around; width: 100%;"> <div style="text-align: center;">  <p>phosphinite</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ HO-P-OH \\   \\ OH \end{array}</math> <p>phosphoric</p> </div> </div> <div style="display: flex; justify-content: space-around; width: 100%;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ CH_3-C-O-P(=O)(O^-)O^- \end{array}</math> <p>acyl phosphate</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ H-P-OH \\   \\ H \end{array}</math> <p>hypophosphorous</p> </div> </div> </div>	<div style="text-align: center;"> <math display="block">\begin{array}{c} R \\ \diagdown \\ P=P \\ \diagup \\ R \end{array}</math> <p>diphosphene</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} H \\ \diagdown \\ P \\ \diagup \\ H \end{array}</math> <p>phosphine</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} X \\   \\ X-P-X \\   \\ X \end{array}</math> <p>phosphide</p> </div>	
<b>SULFUR</b>	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} S \\    \\ R-C-H \end{array}</math> <p>thial</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} S \\    \\ R-C-R \end{array}</math> <p>thione</p> </div> <div style="text-align: center;"> <math>S^{2-}</math> <p>sulfide</p> </div> </div> <div style="display: flex; justify-content: space-around; align-items: center; margin-top: 10px;"> <div style="text-align: center;"> <math display="block">\begin{array}{c} S^+ \\   \\ \diagup \quad \diagdown \\   \end{array}</math> <p>sulfonium</p> </div> <div style="text-align: center;"> <math>R-S-H</math> <p>thiols</p> </div> </div>	<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;">  <p>thiazole</p> </div> <div style="text-align: center;"> <math display="block">^-S-C \equiv N</math> <p>thiocyanate</p> </div> </div>	<div style="display: flex; flex-direction: column; align-items: center;"> <div style="text-align: center;"> <math>R-S-OH</math> <p>sulfenic</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ O=S-S-S-S=O \\    \\ O \end{array}</math> <p>tetrathionate</p> </div> <div style="text-align: center;"> <math display="block">\begin{array}{c} O \\    \\ R-C-SR' \end{array}</math> <p>sulfoxides</p> </div> </div>		<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <math>R-S-S-R</math> <p>disulfide</p> </div> <div style="text-align: center;">  <p>thieno</p> </div> </div>



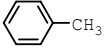

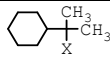

## Molecular Descriptors

Molecular descriptors are the features that distinguish chemical reactivity and provide an organic chemist the necessary information on how to develop synthesis strategies for the preparation of that chemical. Tables S2-S9 provide the molecular descriptors used to represent a certain functional group, and which are used to identify a class of reaction and prioritization of method of addition during synthesis. The below listed descriptors fragmentation key lists and defines the annotations used in representing a molecular descriptor.






### **Descriptors Fragmentation Key**

AA	- Aliphatic attachment
Count	- Represents the amount of same species
<	- Two R groups bonded to an atom
>	- Two R groups bonded to an atom
=	- Double bond
#	- Triple bond
CA	- Carbon attachment
NA	- Nitrogen Attachment
OA	- Oxygen Attachment
PA	- Phosphorous Attachment
SA	- Sulfur Attachment
ANA	- Aromatic Nitrogen attachment
ASA	- Aliphatic Sulfur Attachment
ArA	- Aromatic attachment
ArC	- Aromatic Carbon bond
ArO	- Aromatic Oxygen bond
ArN	- Aromatic Nitrogen bond
ArCN	- Aromatic Carbon Nitrogen bond

**Table S2.** Molecular Descriptors and Fragment Counts for Carbon and Hydrogen Organic Functional Groups.








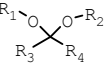
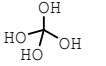

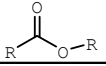
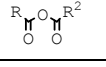
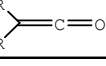



	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Alkanes	$R-R'$	2	CH <sub>3</sub> AA								
Alkenes	$R=CH-R'$	2	CH <sub>2</sub> AA								
Alkynes	$R\equiv C-R'$	2	CH <sub>3</sub> AA								
Alkyl Halide	$R-X$	1	CH <sub>3</sub> AA	1	Cl AA						
Aromatic		6	ArCH								
Arenes		8	ArCH	2	Fused Ar Carbon						
Toluene		1	CH <sub>3</sub> ArA	1	ArC	5	ArCH				
Diene		2	CH AA	2	CH <sub>2</sub> AA						
Haloalkane		5	CH <sub>2</sub> AA	2	CH <sub>3</sub> AA	1	CH AA	1	X AA	1	>C< AA
Cyclo Alkane		6	CH <sub>2</sub> AA								

**Table S3.** Molecular Descriptors and Fragment Counts for Carbon, Nitrogen and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Pyridine		5	CH AA	1	N AA								
Azo	$R-N=N-R'$	2	CH <sub>3</sub> AA	1	N=N								
Alkaloids		3	CH <sub>2</sub> AA	1	CH ArA	1	NH AA	1	AC	4	ACH	1	AN
Imidazole		3	ACH AA	1	AN	1	ANH						
Azide	$N=N=N$	1	$N=[N^+]=N^-$	2	H NA								
Hydrazine	$H_2N-NH_2$	2	NH <sub>2</sub> NA										
Amides		3	CH <sub>3</sub> AA	1	>C=N								
Amines		1	R AA	1	NH AA								

**Table S4.** Molecular Descriptors and Fragment Counts for Carbon, Oxygen and Hydrogen Organic Functional Groups.







	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Alcohol	$R-OH$	1	R AA	1	OH AA						
Ether	$R-O-R'$	2	R AA	1	O AA						
Ketone		2	R AA	1	C=O Ketone AA						
Aldehyde		1	R AA	1	CH <sub>2</sub> AA						
Chroman		2	CH <sub>2</sub> AA	1	CH <sub>2</sub> ArA	1	O ArA	2	ArC	4	ArCH
Methoxy	$MeO-R$	1	R AA	1	CH <sub>3</sub> AA	1	O AA				
Carboxyl		1	R AA	1	COOH AA						
Phenol		1	OH ArA	1	ArC	5	ArCH				
Pyran		5	CH <sub>2</sub> AA	1	O AA						
Epoxide		2	CH <sub>2</sub> AA	1	O epoxide						
Acetal		4	R AA	2	O AA	1	>C< AA				
Orthocarbonic		4	OH AA	1	>C< AA						
Hydrofuran		4	CH <sub>2</sub> AA	1	O AA						
Dicarboxyl	$HCO_2-R-CO_2H$										
Ester		1	C(=O)O AA	2	R AA						
Anhydride		1	C(=O)OC(=O)	2	R AA						
Peroxide	$R^2 \cdot O \cdot O \cdot R^2$	2	R AA	2	O OA						
Ketene		2	R AA	1	C=C=O						
Furan		4	ArCH	1	Aro						
Carbonate		1	OC(=O)O								
Orthoester		2	R AA	1	CH AA	1	O AA	1	OH AA		S9
Peroxide	$H-O-O-H$	2	OH OA								











**Table S5.** Molecular Descriptor and Fragment Counts for Carbon, Nitrogen, Oxygen and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Amides		1	C(=O) nitrogen AA	3	R AA	1	N< AA						
Semicarbazid		1	C(=O) 2 nitrogen AA	1	NH NA	1	NH2 AA	1	NH2 NA				
Imide		2	C(=O) nitrogenAA	2	R AA	1	N< AA	1	CH3 AA				
Amino Acid		1	R AA	1	CH< AA	1	NH2 AA	1	OH AA	1	C=O AA	1	C=CH2 AA
Azole		3	ArCN	1	ArN	1	ArO						
Oxime		2	CH3 AA	1	>C=NOH								
Nitrate		1	ONO2										
Isoxazole		3	ArCN	1	ArN	1	ArO						
hydroxylamine		1	NH2 AA	1	OH NA								
Cyanates		1	N=C=O AA	1	H NA								
Nitro		1	R AA	1	N(=O)	1	O NA						
Nitrite		1	[O]	1	C=O OTHER								
Nitroso		1	CH3 AA	1	N(=O)								








**Table S6.** Molecular Descriptor and Fragment Counts for Carbon, Phosphorous and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Phosphorane		5	R AA	1	P [+5 valence e All single]								
Phosphorine		5	ArCH	1	P								
Diphosphene		2	R AA	2	P								
Phosphine		1	P										







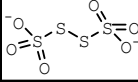
**Table S7.** Molecular Descriptor and Fragment Counts for Carbon, Oxygen, Phosphorous and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Phosphazene		2	R AA	1	P=N								
Phosphonium		4	CH2 AA	4	OH AA	1	P						
Phosphate		3	[O-]	1	P(=O)								
Phosphinite		1	CH3 AA	1	OH PA	2	ArC	1	ArH	1	P [+3 valence e all single]		
Acyl Phosphate		1	C(=O) O-	1	CH3 AA	1	[O]	1	(=O)	1	P(=O)		
Phosphite		3	[O]	1	P[=3 valence e all single]								
Phosphodiester		2	R AA	2	O PA	1	[O]	1	P(=O)				
Phosphoric		3	OH PA	1	P(=O)								
Hypophosphorous		1	OH AA	1	P(=O)								
Phosphide		1	X AA	2	H PH	1	P [+3 valence e all single]						

**Table S8.** Molecular Descriptor and Fragment Counts for Carbon, Sulfur and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Thial		1	C(=S)- AA	1	R AA	1	H CA						
Sulfonium		3	CH <sub>3</sub> AA										
Thione		2	R AA	1	C(=S) AA								
Thiols		1	R AA	1	SH AA								
Sulfide													
Disulfide		2	R AA	2	S SA								
Thieno		1	CH <sub>2</sub> AA	1	CH <sub>2</sub> ArA	1	S- ArA	2	ArC	2	ArCH	1	ArS

**Table S9.** Molecular Descriptor and Fragment Counts for Carbon, Nitrogen, Oxygen, Phosphorous, Sulfur and Hydrogen Organic Functional Groups.

	Structure	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment	Count	Fragment
Thiazole		3	ArCH	1	ArN	1	ArS				
Thiocyanate	$\text{S}^--\text{C}\equiv\text{N}$	1	C#N    alphaticSA	1	S                    AA						
Sulfenamide		3	R    AA	1	N<    AA	1	S    NA				
Sulfate		1	OH    SA	1	S(=O)(=O)    AA	1	[O]				
Sulfones		2	R    AA	1	S(=O)(=O)    AA						
Sulfonate Ester		1	R    AA	1	S(=O)(=O)    AA	1	O				
Sulfoxide		2	R    AA	1	S(=O)            AA						
Sulfenic	$\text{R}-\text{S}-\text{OH}$	1	R                    AA	1	OH                    SA	1	S-                    AA				
Tetrathionate											

## GREEN CHEMISTRY EVALUATION OF SCHEMES A-D

A survey of literature showed that triphenylphosphate has been made via several reaction pathways. Each pathway features a unique chemical inventory including starting materials, intermediates, and waste (byproducts). Although many improvements have been made on the reaction conditions and engineering design, the essential chemicals are the same within a given pathway/mechanism. Therefore, we grouped the reactions by reaction pathway to facilitate the evaluation of green chemistry features. To quantify the green nature and performance of these general reaction schemes, they were characterized by atomic efficiency, yield, and their theoretical yield of byproducts, which is essentially the quantity of waste in a reaction. Various protocols are appended below describing the greenness or associated toxicity issues and energy considerations.

Ilia et al.<sup>1</sup> synthesized triphenyl phosphates by reacting POCl<sub>3</sub> vapor with sodium salts of hydroxyaryl compounds in a vapor-liquid system. In this process, POCl<sub>3</sub> (1 eq) was heated to 70°C and the resulting vapor was carried by a stream of nitrogen into a flask at 20°C containing the hydroxyaryl compound (4 eq) in 20% NaOH solution for a reaction time 40 min. The solid product (**3**) was collected by filtration, washed with 2% NaOH solution followed by water and dried under vacuum. The crude product was then crystallized from petroleum ether (60-80°C) – ethanol to yield 95% of the product. The green aspects of this synthesis include no organic solvent used in the synthesis or extraction phase. NaCl is the only by-product formed and the reaction is carried out at 15-20°C. However, petroleum ether is used for crystallization and is not considered a green solvent.

Luo et al.<sup>2</sup> synthesized triphenyl phosphates by dropwise addition of POCl<sub>3</sub> to a sodium phenolate solution maintaining the reaction temperature below 25 °C. After complete addition of POCl<sub>3</sub>, the mixture was then agitated for 1hr at 25°C and then for 2hr at 40°C. The mixture was cooled; the precipitated

product (**3**) was filtered and washed with water, to afford 92% of the desired product. This method has similar green features as the Ila example previously mentioned.

Sagar et al.<sup>3</sup> utilized microwave (MW) energy in their synthesis of triphenyl phosphates. In this process, the molar ratio of NaOH, phenol, POCl<sub>3</sub> and water of 1:1:0.3:0.03 were mixed in a reaction flask and subjected to MW irradiation (Kelvinator T-37 model) at 100% power for 2min. The ensuing product was extracted with chloroform, washed with 2% NaOH solution and the solvent was removed to generate the product (**3**) in 90% yield. Green aspects of this synthesis are the utilization of an alternate energy source (microwave), for achieving high energy efficiency, and solvent-less reaction conditions. However, chloroform is used for extraction of the product and is considered a hazardous solvent. Distillation is required, to facilitate recovery of the product from the chloroform, which is an energy demanding step and generates hazardous waste. Chloroform is environmental pollutant and is toxic to humans, the target organs liver, kidneys, heart, eyes, skin, and central nervous system. Microwave reactions although performed routinely on a small scale, are notorious for upscaling

Jin et al.<sup>4</sup> used a CH<sub>2</sub>Cl<sub>2</sub> solvent in their synthesis. To a solution of phenol in CH<sub>2</sub>Cl<sub>2</sub>, NaOH was added to produce sodium phenoxide as a thick slurry. A solution of POCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> was added over a period of approximately 2hr at 25°C. Upon completion of the reaction, the mixture was washed with a 10% NaOH solution to remove excess phenol and NaCl. The organic layer was dried and the solvent removed to give the product (**3**) in 91% yield. Greenness for this reaction is carrying out the reaction at 25°C. CH<sub>2</sub>Cl<sub>2</sub> is not a preferred solvent and requires distillation of the solvent to obtain the product and also generates hazardous solvent waste. Dichloromethane is environmental pollutant and is toxic to humans, the target organ is mainly nervous system.

Yang et al.<sup>5</sup> utilized toluene as a solvent medium. In this synthesis, sodium phenoxide is generated by the addition of phenol in toluene to a 20% NaOH (aq) solution. Next, a solution of POCl<sub>3</sub> in toluene was

added over a 30min period keeping the reaction temperature below 25°C. The reaction mixture was then agitated for 30min, the temperature increased to 50-60°C and continued for an additional 20min. Upon cooling the organic phase was separated and washed with water. Toluene and the unreacted phenol were distilled off to provide the product (**3**) in 90% yield. The green feature of this process is the reaction proceeding at lower temperatures. While the use of an organic solvent, toluene, is not favorable; it is a preferred solvent when compared to CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub>. Distillation of toluene, unreacted phenol, and residual wash solutions are high energy demanding processes.

Kore et al.<sup>6</sup> utilized a phase transfer catalyst in their process. An aqueous solution of sodium salt of phenol (12 mmol) in 20mL H<sub>2</sub>O was added to 20mL of chloroform containing the phase-transfer catalyst benzyltriethylammonium chloride, and dibenzo-[18]-crown-6, and the heterogeneous system stirred mechanically. When the organic phase dispersion was stabilized, 3.9mmol of POCl<sub>3</sub> was added dropwise over a 10min period and the reaction continued for an additional 10min. The organic layer was washed with a 2% NaOH solution, dried, and the solvent removed. The crude product was crystallized from petroleum ether and ethyl acetate to give product (**3**) in 90% yield. The greenness of this reaction is the reaction is performed at ambient temperature. However, a hazardous solvent, chloroform, is used. In addition, the process generates waste from the spent phase transfer catalyst and solvent and wash solution waste. Moreover, chloroform and petroleum ether are environmental pollutants and also toxic to humans.

### **Phosphorylation of alcohols via catalysis**

In this process diphenyl chlorophosphate is reacted with phenol in the presence of a Lewis acid (Figure S1). Although this is a one step process as described, the starting diphenyl chlorophosphate itself requires preparation from the basic starting materials such as POCl<sub>3</sub> and phenol. While not captured in the four general schemes presented, this method provides a sample of a process for the synthesis of unsymmetrical phosphates.



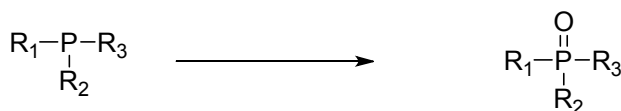


**Figure S1:** Synthesis of triphenyl phosphates *via* catalysis

Ranu et al.<sup>7</sup> described a procedure for phosphorylation of alcohols catalyzed by  $\text{InCl}_2$ . A molar ratio of phenol, diaryl chlorophosphate and  $\text{NEt}_3$  of 1:1.5:2.5 were reacted in the presence of  $\text{InCl}_2$  at  $25^\circ\text{C}$  for 2hr. The reaction was then quenched with water and extracted with ether. The ether extract was washed with brine, dried and the solvent removed to provide the crude product which was then purified either by micro distillation or column chromatography to yield 81% of the pure product (**3**). The green aspects are the use of ambient temperature reactions conditions and a catalyst rather than stoichiometric reagents. Ethyl ether, used for product extraction is not a green solvent and an environmental pollutant. Distillation of any solvents used and for product purification is required, generating hazardous solvent waste and requiring significant amounts of energy. Aqueous Indium containing waste and phenol may require special disposal considerations, adding extra economic cost.

Jones et al.<sup>8</sup> accomplished the same reaction but using  $\text{TiCl}_4$  as a catalyst. In this process, reactions performed under a nitrogen atmosphere at  $25^\circ\text{C}$  for 1hr with  $\text{TiCl}_4$  (2mol%) in the presence of  $\text{NEt}_3$  in THF. The molar ratio of phenol, diphenyl chlorophosphate, and triethyl amine used in the reaction were 1:1.5:1.5. The product (**3**) was produced and isolated in 98% yield. This process has similar green features as mentioned above. However, THF is not a preferred solvent.

#### Oxidation of triphenyl phosphite (Scheme B)



**Figure S2:** Synthesis of triphenyl phosphate *via* oxidation of phosphites (Scheme B)

In this methodology (Scheme B), triphenyl phosphite is oxidized to triphenyl phosphate using various reagents and a few examples are provided below (see Figure S2). Although this is a one-step oxidation process, the starting phosphite needs to be prepared from the basic chemicals,  $\text{PCl}_3$  and phenol.

Peng et al.<sup>9</sup> accomplished the oxidation of phosphite using  $\text{HOF} \cdot \text{CH}_3\text{CN}$ . In this process, phosphite (2mmol) in dichloromethane (5mL) at  $0^\circ\text{C}$  was added to  $\text{HOF} \cdot \text{CH}_3\text{CN}$  solution (4mmol) and vigorously stirred at  $0^\circ\text{C}$  for 5min and the reaction immediately quenched with a sodium bicarbonate solution. The reaction mixture was extracted with dichloromethane, and the organic layer washed with a saturated NaCl solution, dried over sodium sulfate and the solvent removed to provide virtually pure phosphate in 100% yield. The starting reagent requires preparation with  $\text{F}_2$  (g) and  $\text{CH}_2\text{Cl}_2$  as a reaction solvent, both are hazardous, and their use is not recommended. Distillation is required, to facilitate product recovery from  $\text{CH}_2\text{Cl}_2$ , which is an energy demanding step and generates hazardous waste.

Oba et al.<sup>10</sup> carried out the oxidation of phosphite using photolysis in the presence of a telluride reagent. A 0.1M  $\text{CH}_3\text{CN}$  solution of triphenyl phosphite containing bis(2,4,6-triisopropylphenyl)telluride ( $\text{Tip}$ )<sub>2</sub>Te, 1mol%) and rose Bengal was irradiated under aerobic conditions with a 500 W halogen lamp at  $50^\circ\text{C}$  for 2.5hr. NMR analysis showed quantitative conversion to triphenyl phosphate and the product (**3**) was isolated in 92% yield. The use of photolysis and acetonitrile, a moderate solvent choice, can be considered greener aspects of this example. However, ( $\text{Tip}$ )<sub>2</sub>Te requires prior preparation is expensive. The Te waste generated during the work up process might require special disposal considerations.

Mukaiyama et al.<sup>11</sup> utilized a solution of triphenyl phosphite (0.01mol) in 10mL ether which was added dropwise to a suspension of monobromocyanoacetamide (0.01mol) and benzyl alcohol (0.01mol) in 20mL ether with vigorous overnight stirring at room temperature. The precipitated cyanoacetamide by-product was filtered. Ether was removed from the filtrate to produce a residue which was distilled to give benzyl bromide (73%) and triphenyl phosphate (90%). The green considerations for this reaction are room

temperature reaction conditions. However, the reaction solvent ether is not a preferred solvent and an environmental pollutant. The oxidation reagents are used in equimolar ratios; thus, by-products are formed in similar ratios detracting from the attractiveness of this synthetic route. Distillation of the crude product is needed to remove the by-product benzyl bromide is high energy demand process and results in the generation of hazardous waste.

Power et al.<sup>12</sup> used gallium peroxide for this oxidation process. To a pentane solution of gallium peroxide (1g, 2.11mmol in 30mL) was added triphenyl phosphite (0.96mL, 4.22mmol) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the residues were determined by proton and phosphorus NMR (no isolated information but in the text claims quantitative conversion). Ambient reaction temperature conditions contribute to the greenness of this reaction. The gallium peroxide reagent used is not commercially available and requires its preparation adding to its cost. Pentane is not an environmentally friendly solvent and also requires distillation. Gallium waste generated may require special waste disposal considerations, also adding cost to this route.

Dibella<sup>13</sup> used a mixture of iodine and iron chloride for this oxidation process. Triphenyl phosphite (710g, 2.29mol), iodine (1.78g, 0.007mol) and iron (III) chloride (2.34g, 0.014mol) were charged in a stainless steel Parr autoclave vessel. The mixture was heated to 115-120°C with efficient agitation and pressurized with O<sub>2</sub> at 55psig. The oxygenation was continued until no oxygen pressure drop was observed (5hr). The crude solid product (**3**), formed in nearly quantitative yields, was washed with a sodium bisulfite solution followed by a dilute sodium carbonate to remove the catalyst components prior to a distillation step. The features which add greenness are iodine and iron chloride are used in catalytic amounts and the reaction is achieved in the absence of any solvent. The aqueous waste generated does not require any special disposal requirements. However, the reaction carried out elevated temperature and high oxygen pressures, lending to combustible conditions in addition, the purification of the product by distillation is a very high energy demanding process.

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